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CONTENTS

Multiple Sclerosis and "Encephalomyelitis" 301
Tracy J. Putnam

The Management of Hypertension 317
William Goldring

Pulmonary Irritants 340
Robert A. Kehoe

The Effect of War Gases and Other Chemicals on the Eyes of the Civilian Population 356
Conrad Berens and Edward Hartmann

Library Notes:

Recent Accessions to the Library 368

Deaths of Fellows 369

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

MAY, 1943

MULTIPLE SCLEROSIS AND "ENCEPHALOMYELITIS"*

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HISTORICAL

ABOUT a century ago, in 1836 or 37,[1] Sir Robert Carswell, Professor of Pathology at the University of London, published an installment of his handsome atlas of pathology[2] containing a picture and description of a most interesting neurologic specimen. The pons and cord were spotted with greyish areas of atrophy of irregular shape, and in the lumbar region was an area of softening. No history was available.

Within a year or two, the great French pathologist, Cruveilhier, described three similar specimens in his own atlas of pathology,[3] also coming out in installments. His description was far more complete than Carswell's and in addition, he was able to supply two typical case histories.

During the following twenty years, there were sporadic anatomical and clinical studies of the various types of degeneration of the spinal

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cord. An example is a clearly written pathologic report by a young Philadelphian, Dr. S. Weir Mitchell. But little progress was made toward a practical working knowledge of this peculiar disease, until the publication in 1868 of a clear, concise review of the literature and description of original cases by Jean Marie Charcot.[4] He definitely fixed the name of the disease—"Sclérose en plaques disseminée"—and gave a succinct account of the pathologic changes, which is in certain ways better than the descriptions in some modern textbooks. He emphasized the haphazard distribution of the lesions, their sharp outlines, the breakdown of myelin sheaths, the preservation of a variable proportion of axis cylinders, the glial scar, and the thickening and obstruction of vessels.

His description of the clinical picture was clear, though oversimplified. It was based on the illness of a servant girl in his own household, who finally came to autopsy at the Salpêtrière. Her symptoms—nystagmus, intention tremor and scanning speech—constitute the triad familiar to every medical student. In a later work (1879), Charcot[5] went further, and called attention to the milder cases, which we now recognize as the commonest type.

Charcot's lectures on neurology became known all over the world, and doubtless as a result, a steadily increasing number of cases of multiple sclerosis began to be reported. In the last century, it was considered to be a rare disease, but modern statistics show it to be a common one, especially if we include its acute forms, usually known as encephalomyelitis, acute transverse myelitis and optic neuritis.

Prevalence of multiple sclerosis and related disorders: Owing to variations in standards of diagnosis and in local prevalence, it is extremely difficult to estimate the incidence of multiple sclerosis. A survey in Switzerland showed 7 per 10,000 in certain localities.[6] In recruits examined for the last war, the incidence was about 1 per 10,000 (including rejections and discharges). The last figures for selectees in the New York City area showed a rate of rejection of about 6 per 10,000 for multiple sclerosis, encephalitis and myelitis. These figures are probably all on the low side, for recent experience shows that the diagnosis is more often missed than erroneously made. With the use of modern refinements in diagnosis, multiple sclerosis and encephalitis need no longer be "wastebasket" categories.[7] It is clear that in this locality at least, multiple sclerosis is by no means a rare disease.

There is a pronounced difference in the *local* incidence of multiple sclerosis. It is common in the Baltic countries, Scotland, the North Atlantic seaboard and the Great Lakes region. It is rare in the Mediterranean countries and our own South, and almost unknown in China, Turkey, India and Japan.

Scope of the category of demyelinating diseases: Multiple sclerosis as ordinarily defined, is characterized pathologically by the existence of glial scars scattered throughout the nervous system. There is now practically complete agreement among neuropathologists that the gliosis is secondary to tissue damage, and that each lesion goes through an acute stage (Marburg[8]). It is usually agreed that the acute lesions are marked by edema and local glial proliferation and perivascular infiltration.

Beyond this point, there are many differences of opinion, and here I can do no more than express my own. I believe, with Marburg,[8] Ferraro,[9] Juba[10] and a few others, that the disorders characterized by scars interspersed with acute lesions are but the chronic relapsing form of the acute demyelinating diseases (Figures 1, 2). This group of diseases includes the type known as post-infectious and disseminated encephalomyelitis, Schilder's disease, diffuse sclerosis, neuromyelitis optica, acute transverse myelitis, and "idiopathic" optic and retrobulbar neuritis.[11] The histopathology of these disorders is fundamentally uniform;[9,10,11,12] the differences are in location and intensity of the lesions Naturally, an acute transverse lesion of the cord is more apt to be fatal than one in the optic nerve; naturally also, massive lesions of both hemispheres (Schilder's disease, diffuse sclerosis) is more devastating than small isolated plaques, but the type and varieties of tissue reaction are the same. The acute disorders comprise the great majority of the cases of "encephalitis" encountered in practice; the specific encephalitides, due to known infective viruses, present a wholly different aspect, pathologic and clinical, and are at present rare in this region.

Since there is no agreement whatever among neuropathologists as to the etiology of these disorders, I shall postpone consideration of it until after a sketch of their clinical manifestations, which should be taken into account in deciding among rival theories.

Predisposing factors—Infections: Taking the demyelinating diseases as a group, it is clear that a sudden or subacute onset is common and often apparently precipitated by exogenous factors. This is most clearly

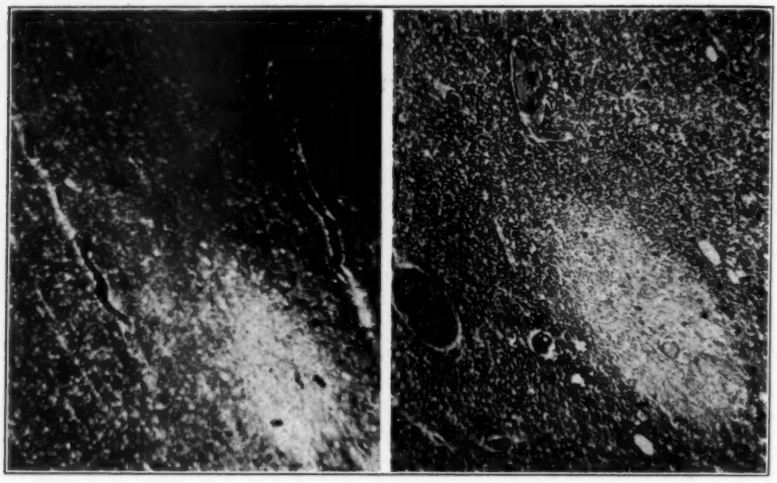

Fig. 1 Fig. 2

Fig. 1—Multiple sclerosis. A small, early lesion, consisting of loss of myelin, damage to axis cylinders, and glial proliferation. Note the tortuosity and engorgement of the veins draining the area. Mallory's connective tissue stain.

Fig. 2—Postvaccinal "encephalitis." Early demyelinating lesion. Note the similarities to Figure 1. The thrombosis of the neighboring vessels is obvious. Mallory's connective tissue stain.

seen in the post-infectious "encephalomyelitides." In the post-vaccinal form, the onset of the "encephalitis" coincides with the height of immunity in most cases; that is, it occurs on the 11th day in most cases.[13] In post-measles "encephalitis," the onset of cerebral symptoms usually occurs in five days from the outbreak of the rash. While these two types of post-infectious "encephalitis" are the most widely recognized, they are not the most common. Actually, the banal infections of the respiratory tract—pneumonia, sinusitis, tonsillitis—are more often the apparent precipitating cause of optic neuritis, "encephalomyelitis," acute transverse myelitis, neuromyelitis optica, and multiple sclerosis, than are any of the specific infectious diseases.[14]

Examples should be familiar to all practitioners. An instance is the following:

J. M., a previously healthy medical student, developed a paronychia of the middle finger of the left hand in 1927. Three days later, he came down with a quadriplegia and symptoms of bulbar disease, and had to be tube-fed. There was an increase of

cells in the spinal fluid. A diagnosis of "encephalitis" was made. After a convalescence of several months, he considered himself entirely well and returned to work. Following a period of fatigue, he developed a paronychia on the other hand, and had a recurrence of the same symptoms. He recovered from this also, but with a residual limp and hemiataxia. He graduated from medical school and went into practice. Every year or so, he has an attack of sinusitis, and his weakness and ataxia reappear. Each attack leaves him slightly worse, and sometimes adds a new symptom, but he is still able to practice.

Syphilis should probably be included among predisposing infections. The incidence of serologic evidences of syphilis is slightly higher among patients suffering from multiple sclerosis, than in the population at large.

Trauma: Acute traumatic "encephalomyelitis" is a recognized disease entity, but it is relatively rare. Adler[14] found two cases, compared with thirty following infections. The influence of injury is apparent in many cases of multiple sclerosis, however. Some striking examples are the following:

The R. sisters were identical twins, aged 27, who earned their living by tap-dancing at night clubs. Shortly after finishing an engagement, one of them slipped and fell, landing on her buttocks. She was certain that she felt perfectly steady and normal up to the time of the fall; but at once she felt a weakness of the legs, and a numbness up to the nipples. She had to be helped home. A neurologist was called, and found bilaterally positive Babinski signs. From that on, she ran an intermittent downhill course, finally presenting an unmistakable picture of advanced multiple sclerosis. The other twin remains in good health.

A female schoolteacher of 28 was brushed by a passing automobile and thrown down, but was not unconscious. She was unable to rise, and had to be taken to the hospital. There she was found to have a mild paraplegia, intention tremor and nystagmus. She had been incapacitated for three months when last seen.

Pregnancy and Menstruation: A fatal "encephalomyelitis" is apparently rare in pregnancy, but few women who have had retrobulbar neuritis or other manifestations of multiple sclerosis can pass through pregnancy and the puerperium without danger of an exacerbation.[15] Initiation or exacerbation of multiple sclerosis occurred in 60 per cent of Beck's female patients[16] who had borne children, and this corresponds with my own experience. Similarly, menstruation has an adverse effect, particularly in the terminal stages of the disease.

Thus, one woman (in whom the diagnosis was confirmed at autopsy) began to have irregular periods toward the end of her course. Preceding each one she would have a two days' fever, and become completely paralyzed, often unconscious. Each of these events marked a step downward in the progress of her disease, which was practically stationary between them.

Toxic Substances: "Encephalomyelitis," "myelitis" and multiple sclerosis are not infrequently precipitated by the administration of sera, vaccines, and certain chemicals. In a case in my collection, an acute paraplegia followed the day after a vaccination against typhoid fever

and similar cases are reported in the literature.[17] The incidence of "encephalomyelitis" during the Pasteur treatment against rabies is about .04 per cent (Wilson[18]). Tetanus antitoxin[19] (and experimentally tetanus toxin[20]) have also apparently been responsible for the onset of multiple sclerosis. I have seen two cases in which relapses followed immediately upon administration of histamine. Perhaps the case of "encephalitis" following a burn, reported by Globus and Bender[21] belongs in this category also. In animals, coagulants produce a similar picture.[22]

Of inorganic substances, the injection of sulfanilamide has been followed by a typical "encephalomyelitis."[23] Carbon monoxide poisoning has precipitated a progressive multiple sclerosis.[24] Experimentally, repeated administration of potassium cyanide rather regularly brings about the characteristic pathologic changes.[25] Lead poisoning has been found in multiple sclerosis,[26] and excessive amounts of arsenic in cases of "encephalomyelitis."[27] Finally, the typical "hemorrhagic encephalitis" produced by arsphenamine, and some of the cases of carbon monoxide and nitrous oxide poisoning, closely resemble post-infectious "encephalomyelitis."

Other Factors: Over-exertion, chilling, fright and emotion are often mentioned as precipitating causes of multiple sclerosis, and von Hoesslin[28] gives some rather low figures of incidence. In the category of emotion (rather than of trauma) might go the cases in which lumbar puncture or venipuncture have apparently brought on exacerbations of an established multiple sclerosis. This I have seen.

Brickner and Brill[29] have cited cases in which dietary indiscretions or the use of a greatly restricted diet have been followed by relapses. This I have not happened to observe. The possible influence of diet will be considered under etiology.

Manifestations: There is no single syndrome that can be considered typical of multiple sclerosis and the demyelinating diseases. A great variety of symptoms may occur: Weakness or numbness of one or more extremities, tremor, ataxia, nystagmus, speech disturbances, emotional lability, retrobulbar neuritis or papillitis, with central scotoma, diplopia, disturbances of bladder function and the "electric phenomenon" are frequently found in both the acute and the chronic stages of the disease. Less well recognized are various psychoses,[30] convulsions,[31] decrease in potency, papillitis, symptomatic paralysis agitans,[32] trigeminal neuralgia,[33] sciatica and other neuritic pains, headache, mus-

cular atrophy,[34] oscillopsia,[35] drowsiness, difficulty in swallowing, hemianopia, and aphasia. An outstanding review of the manifestations of multiple sclerosis may be found in Marburg's monograph.[36]

In the acute, fulminating cases of "encephalomyelitis," fever, headache, convulsions, coma, stiffness of the neck, hemiplegia, oculomotor palsies, and acute optic neuritis are common (Adler[37]).

The course of symptoms is often characteristic. They sometimes come on within a few minutes, or overnight. A patient may watch a scotoma develop, or be thrown down by a hemiplegia. Often, the onset is subacute, gradually increasing over days, sometimes with fever and leukocytosis. Even when symptoms come on insidiously, the patient is able to remember slight variations in progression. Once at their height, symptoms tend to improve or disappear. If relapses occur, they more often consist of an exacerbation of existing symptoms, than of the appearance of new ones, though both may concur.

A single isolated "signal symptom," such as numbness of one extremity, diplopia, or central scotoma, may appear and disappear long before the disease as a whole becomes recognized.

In analysis of symptoms and signs, the important points for diagnosis are *evidence of lesions scattered in time and space.* Most of the lesions affect white matter, so that signs of injury to the cortico-spinal, cerebellar and vestibular systems are common. The lesions are rarely complete over large areas, so that gross sensory defects are unusual (except in acute stages). Paraplegia with a sensory level is not rare, usually as a terminal event. Grey matter suffers less than white matter, so that convulsions, muscle atrophies, and nuclear palsies are unusual; but the more fulminating the onset, the less the lesions respect nerve cells.

Examination of the spinal fluid is of great help in diagnosis. In multiple sclerosis according to Merritt,[38] the cells are increased beyond 5 in 28 per cent of cases, but rarely over 100. Protein is increased in 24 per cent of cases. Abnormal gold sol curves are found in 71 per cent of cases. A slight increase of pressure is occasionally recorded. In only 17 per cent of cases is the fluid entirely normal. Naturally, examination of the spinal fluid is of great help in ruling out syphilis and tumor.

A somewhat different picture is found in fulminating cases of "encephalomyelitis." The cell count is usually higher, and may reach 8,000. Pressure is occasionally elevated. The protein is rarely much elevated, and a frankly positive gold sol curve is practically never found.

TABLE I

PRINCIPAL SYMPTOMS IN 183 CASES OF MULTIPLE SCLEROSIS

	AS FIRST SYMPTOM		AS SUBSEQUENT SYMPTOM	
	Total	*Improved*	*Total*	*Improved*
Paraplegia	19	9	70	22
Ataxia; tremor	23	10	44	15
Monoplegia	24	13	33	18
Scotoma	20	16	32	20
Numbness of one extremity	20	15	26	13
Bladder symptoms	6	4	39	15
Diplopia	18	12	24	14
Numbness of both legs	7	5	19	15
Disturbance of speech	2	2	22	4
Mental deterioration	2	0	16	1
Hemiparesis	6	3	11	5
Pain (radicular)	1	0	13	5
Hemianesthesia	5	4	4	4

If the patient survives this acute phase, the spinal fluid picture gradually becomes that typical of multiple sclerosis.[12]

Spinal punctures (and other procedures such as encephalography or even venipuncture) are sometimes followed by exacerbations—doubtless a non-specific effect.

Visual fields should be plotted in every suspected case. The presence of a central or ceco-central scotoma, even relative, is characteristic.

Electroencephalography is sometimes useful. In cases in which only paraplegia or ataxia are evident, a cerebral focus may be revealed. Fluctuations in the extent of an area of phase reversal may be the clearest manifestation of the typical remissions and exacerbations.

A cystometrogram often furnishes additional objective evidence of a lesion of the cord.

Psychometric studies are helpful in assessing prognosis and ability to work. The record of achievement is usually spotty and variable.

Course and Prognosis: The diagnosis of multiple sclerosis is usually

considered to be worse than a sentence of death. Thus, Osler's textbook states that "ultimately, the patient, if not carried off by some intercurrent infection, becomes bedridden." Certainly all of us have seen patients in the late stage of the disease, helpless and miserable, yet clinging to life often for a decade or two.

On the other hand, a survey of a large series of cases shows that remissions are common, and substantial spontaneous recovery is not rare. Von Hoesslin[28] found 17 per cent of remissions among his 516 cases, lasting for periods up to forty-five years. Dr. Brown and I reviewed 133 cases which we had personally observed,[7] and found that some improvement occurred at some time in ninety-two of them. Twenty per cent were working, 47 per cent were ambulatory, 15 per cent were helpless, and 12 per cent were dead. It was clear, moreover, that certain symptoms carried in themselves a better prognosis than others. Data for the more common symptoms are given in Table I.[7]

The following conclusions resulted from the detailed study.

1. The prognosis is better for early symptoms than for late ones—hence, of course, the transient character of the "signal symptoms."

2. Symptoms evidently due to small lesions, such as diplopia, central scotoma or sensory disturbances of one extremity, tend to regress within a few months, while symptoms due to larger lesions such as paraplegia, ataxia and mental deterioration are usually permanent.

3. Isolated symptoms disappear in a far higher proportion of cases than do the same symptoms occurring in conjunction with others (usually therefore due to large lesions).

4. Symptoms tend to grow more severe as the disease progresses.

5. Cases in which severe symptoms occur at the outset, usually run a much more malignant course than those in which the early symptoms are mild and transient. There are, however, many exceptions to this rule.

6. Cases seen in office practice tend to do much better than those seen on hospital wards. Periods of improvement were found in 87 per cent of the former and in only 62 per cent of the latter.[7] Whether this is because ward patients have more severe symptoms at the outset, or whether it is due to differences in economic level, the fact is undoubted.

While the survey did not bring out the point clearly, it is widely believed by neurologists that the course of the demyelinating diseases is more stormy ("encephalitic") in children, more gradual in middle

life. An onset after 40 is somewhat unusual, but may occur.

Etiology and Mechanism of the Disorder: All the information we can muster is still too scanty to give a complete picture of the pathogenesis of multiple sclerosis and the "encephalitides."

Some general possibilities can at once be ruled out. It is not primarily a hereditary disease. Thums[39] has traced 14 pairs of identical twins, of which one had multiple sclerosis; in no instance was the other affected. (This paper adds a 15th pair). There are, to be sure, occasional instances in which two cases have occurred in the same family, but they are probably to be ascribed either to coincidence, or to confusion with hereditary ataxia which sometimes closely simulates multiple sclerosis.

Multiple sclerosis and the related disorders are not deficiency diseases. They are rarest where dietary deficiencies are most prevalent—namely, in China and our own Southern states. Attempts at treatment with high vitamin diets and injections of liver extract were begun fourteen years ago at the Boston City Hospital, and were abandoned when it became clear that the course of the disease was unaffected.[40] More recently, intensive treatment with a wider variety of vitamins (including vitamin E) at the Neurological Institute has yielded equally negative results.

It is extremely unlikely that multiple sclerosis and the demyelinating "encephalitides" are due to a living virus. The pathologic changes are entirely distinct from those resulting from known specific infections; for example, poliomyelitis and equine encephalitis.[41] Although countless attempts have been made to transmit the disease to animals, by many bacteriologists including Noguchi, all have been negative; not a single one of Koch's postulates have been fulfilled. The presence of spirochetes in the lesions has been occasionally reported, but competent observers have failed to corroborate the observation.[42] Schaltenbrand's recent brief note,[43] reporting production of a disease in animals not resembling multiple sclerosis, is unsatisfactory in many respects.

Meanwhile, some positive evidences indicating an entirely different type of etiology have gradually accumulated.[44,45] Lesions closely resembling those of "encephalomyelitis" in the acute stage, and those of multiple sclerosis in the chronic stage, have been produced by obstruction of cerebral venules.[45] Similar lesions may be brought about by injection of coagulants[22] or of asphyxial poisons.[25] Thrombi are found regularly in acute lesions, both of "encephalomyelitis" and of

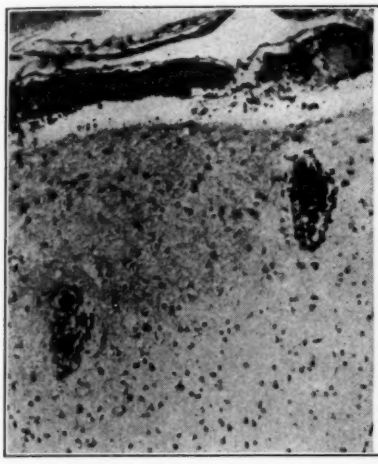

Fig. 3

Fig. 4

Fig. 3—Muitiple sclerosis, with death in an acute exacerbation. Two small thrombosed veins draining a plaque. Mallory's connective tissue stain.

Fig. 4—Muitiple sclerosis. Fresh thrombus in a vein adjacent to a plaque. Mallory's connective tissue stain.

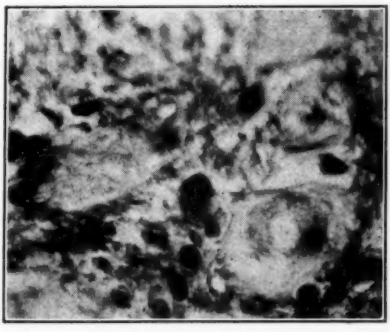

Fig. 5—Multiple sclerosis. Fibrous cords representing the remnants of obstructed vessels, adjacent to the lateral ventricle. Mallory's connective tissue stain.

multiple sclerosis (Figures 3, 4, 5) and in other organs of the body.[44] There is a peculiar lability of the clotting mechanism in cases of multiple sclerosis.[46,47]

All these facts may be fitted together in some such theory as the following: There are individuals who suffer from a peculiar lability of the clotting mechanism of the blood. Whether this is congenital or acquired is not clear. If it exists, however, any slight disturbance of

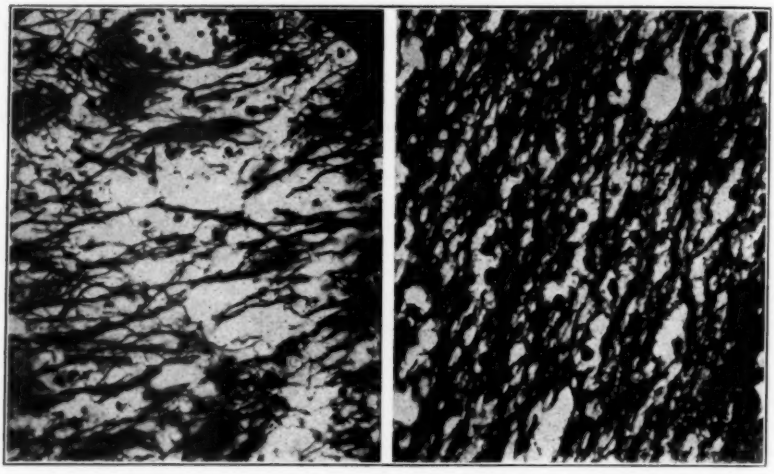

Fig. 6—Multiple sclerosis. Axis cylinders within a plaque (left), and in relatively normal adjacent tissue (right).

the equilibrium of the body may precipitate a shower of minute thrombi in various tissues. Most of these cause no permanent damage, but any that occur in the brain leave a permanent landmark behind and a local vascular abnormality which predisposes to further clotting. If the process is sufficiently stormy, a widespread destruction is produced, and the patient dies with the manifestations of "encephalomyelitis." Limitations of space forbid going into further details, but they may be found in some of the references already cited.

Treatment: A study of the lesions of multiple sclerosis makes it clear that a large proportion of axis cylinders are destroyed in the acute phase of the process[48] (Figure 6). The larger the lesion, and the longer the disease has continued, the more severe the damage to axons. A useful regeneration of axis cylinders in the central nervous system is at present inconceivable. It follows, therefore, that no treatment (beyond ordinary regulation of hygiene) can be expected to influence the course of lesions which have already occurred.

This conclusion is borne out by a statistical study of the effects of the various forms of treatment now in use.[40] The average rate of improvement closely approximates that found in untreated cases.

These facts, and the theory of pathogenesis just outlined, do not necessarily mean that all attempts at treatment are hopeless. They do, however, imply, *that a given treatment should be judged not on the basis of its effect on existing symptoms, but on its success in preventing relapses.* If exacerbations can be definitely prevented, the normal tendency is to recovery.

This goal does not seem permanently out of reach. There are several steps toward it which are always worth considering.

In the first place, possible precipitating causes should be avoided when possible. A search should be made for focal infections. The patient should be protected against over-exertion and accidents, as far as possible. Female patients should avoid pregnancy.

In the second place, advantage should be taken of the regional differences in incidence of the disorder when circumstances permit. Life in a warm, dry climate seems to have a beneficial effect on many cases—possibly because the common infections of the nose and throat are less prevalent there. Unfortunately, this form of treatment is out of the reach of most patients.

In the third place, a constant search should be made for means of correcting the instability of the plasma. The use of anticoagulants naturally suggests itself; and actually they can be shown to have an effect on some experimental forms of the disease.[22] None of the anticoagulants given by vein (for example, heparin) seem promising. Cysteine is a feeble anticoagulant,[49] which has seemed to afford some protection to some patients. By far the most promising substance seems to be dicoumarin,[50] and it is now being tried on a series of cases.

Meanwhile, symptomatic treatment should not be forgotten. The patient's health and strength must be maintained in every possible way. If spasticity is annoying, small doses of bromides are sometimes useful. Alcohol in moderation may help the patient's spirits, and paradoxically, his balance if ataxia and tremor are present. The use of sandalwood oil and of tincture of belladonna is often helpful in cases of urgency. An important point is that the urgency will often pass off if the patient makes up his mind to disregard it or distracts his attention to some other task. In cases in which the bladder disturbances are of long standing or accompanied by infection, periods of tidal irrigation[51] are often extremely helpful. Patients with hemiataxia may learn to avoid staggering by habitually leaning toward the more normal side. The disagreeable

sensation of slapping the ground with the toes which is a common component of the spastic gait may often be mitigated by practice in placing the heel on the ground first, then rolling the weight along the outer edge of the foot to the toe. A brace may be worn for toe-drop. Subarachnoid alcohol injection or root section may be needed for radicular pains or for contractures in bedridden patients. The foot placement exercises so useful in tabes, are often of benefit in multiple sclerosis also. Special telescopic lenses are available for patients whose loss of vision is relatively fixed and constitutes the most disabling symptom. Motorized wheel chairs may be of use for those unable to walk.

Conclusion

Multiple sclerosis is often regarded as a "rare and mysterious disease." It is certainly not rare, and it is much less mysterious than it once was. A careful, patient analysis of the remaining problems, step by step, gives promise of revealing the roots of the disorder. Even with what we know already, the directions which a rational system of treatment should take is already fairly clear.

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THE MANAGEMENT OF HYPERTENSION*

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THE treatment of essential hypertension has passed through two periods; an empirical period during which treatment consisted of administration of vasodilator and other hypotensive drugs and a second period, which brings us up to date, during which treatment presumes to be based upon knowledge of the causative mechanism.

During the period of empiricism, drugs have varied from the evanescent vasodilator nitrites through the ineffectual extracts of watermelon seeds and garlic up to the dangerous thiocyanate. These forms of therapy have had little effect on the individual sufferer and no effect on the incidence of hypertensive disease; nor was any significant addition made to the understanding of the underlying mechanism of essential hypertension. Because of the recent revival of interest in thiocyanate I will review our experience.

In 1932 Dr. Chasis and I[1,2] studied the effect of thiocyanate in hypertension on the wards of the Third Medical Division of Bellevue Hospital, and the Nephritis and Hypertension Division of the New York University Medical College Clinic.

Tables I and II give a summary of the results of treatment in an ambulatory and a hospitalized group of patients with essential hypertension. There were forty-four trials in the ambulatory group and twenty-five trials in the hospital group. The ages ranged from 29 to 65 years. The period of control in the ambulatory group ranged from 7 to 378 days and in the hospital group from 5 to 105 days. It will be noted that a "trial" was considered effective when the blood pressure fell to, or below, 165 systolic and 100 diastolic, arbitrarily chosen as our criterion. There are instances (see cases 20, 24 and 41, Table I, and cases 11, 14 and 15, Table II) in which marked falls in both systolic and diastolic pressure occurred, but the blood pressure remained distinctly

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TABLE I

RESULTS OF TREATMENT WITH THIOCYANATE IN ESSENTIAL HYPERTENSION: AMBULATORY GROUP

No.	*Age*	*Blood Pressure Control*		*Control Period, Days*	*Lowest Blood Pressure after Treatment*	*Thiocyanate Intoxication*	*Effective in Lowering Blood Pressure*
		Range, Mm. Hg	*Average, Mm. Hg*				
1	54	220/110 to 198/104	213/107	126	150/ 85	No	Yes
2	54	220/110 to 190/104	190/104	161	165/ 90	No	Yes
3	64	220/120 to 185/100	205/109	35	140/ 70	No	Yes
4	65	230/138 to 175/104	203/116	294	190/ 92	Yes	No
5	46	260/130 to 210/110	252/120	378	185/ 95	No	No
6	56	205/120 to 170/ 98	180/105	231	135/ 70	Yes	Yes
7	37	240/140 to 188/106	203/122	273	158/ 95	No	Yes
8	53	236/156 to 198/120	220/136	182	157/ 90	No	Yes
9	53	215/125 to 175/115	196/117	35	150/ 75	No	Yes
10	53	205/120 to 174/105	190/113	14	145/ 90	No	Yes
11	29	268/132 to 180/132	206/132	133	180/125	No	No
12	29	268/132 to 180/132	198/132	168	185/125	Yes	No
13	29	268/132 to 180/132	190/130	203	150/110	No	No
14	50	210/120 to 160/108	174/112	33	155/ 95	No	No
15	42	260/160 to 132/ 80	187/122	53	207/127	No	No
16	38	182/145 to 168/135	177/140	14	180/125	No	No
17	58	212/122 to 196/109	203/116	84	165/105	No	No
18	61	224/130 to 198/110	210/119	35	192/105	No	No
19	62	240/125 to 200/ 96	217/109	91	158/ 90	No	Yes
20	51	222/142 to 216/140	218/141	28	184/112	No	No
21	46	250/118 to 195/100	222/109	62	184/ 90	No	No
22	64	210/ 88 to 190/ 88	198/ 88	32	150/ 75	No	Yes
23	53	230/125 to 170/110	206/121	48	170/ 98	No	No
24	40	250/130 to 232/120	239/123	42	186/106	No	No
25	46	225/110 to 184/ 96	209/103	84	190/100	No	No
26	62	206/100 to 188/ 92	200/ 96	28	164/ 82	No	No
27	65	212/110 to 160/ 90	186/101	111	178/ 94	No	No
28	54	212/104 to 198/ 94	206/ 97	42	170/ 90	No	No
29	45	200/128 to 185/102	192/115	56	174/ 96	No	No
30	54	210/118 to 165/100	182/100	133	188/108	No	No
31	42	199/125 to 190/108	196/116	21	178/110	No	No
32	51	250/158 to 184/110	243/129	203	164/120	No	No
33	55	250/140 to 180/ 98	200/110	67	156/ 96	No	No
34	62	235/130 to 180/115	208/123	28	215/110	No	No
35	46	260/130 to 185/ 92	215/110	469	166/ 90	No	No
36	64	215/120 to 160/180	200/105	28	150/ 72	No	No
37	63	230/138 to 175/ 95	205/110	220	190/ 90	No	No
38	54	220/120 to 165/100	195/105	168	175/108	No	No
39	46	250/118 to 170/ 94	185/102	54	176/110	No	No
40	64	216/ 96 to 184/ 78	199/ 88	91	142/ 70	No	Yes
41	50	218/126 to 212/122	215/124	7	182/100	No	No
42	53	220/120 to 170/ 98	180/110	90	200/112	No	No
43	40	234/128 to 186/106	205/105	180	186/104	No	No
44	56	230/125 to 180/100	209/119	360	190/ 90	Yes	No

TABLE II

RESULTS OF TREATMENT WITH THIOCYANATE IN ESSENTIAL HYPERTENSION: HOSPITALIZED GROUP

No.	*Age*	*Blood Pressure Control*		*Control Period, Days*	*Lowest Blood Pressure after Treatment*	*Thiocyanate Intoxication*	*Effective in Lowering Blood Pressure*
		Range, Mm. Hg	*Average, Mm. Hg*				
1	50	210/120 to 160/108	174/112	15	160/100	No	No
2	53	232/134 to 198/125	209/129	8	129/ 70	No	Yes
3	46	208/120 to 190/108	194/114	35	170/110	No	No
4	57	230/130 to 186/ 92	202/113	11	118/ 90	Yes	Yes
5	53	236/134 to 196/120	220/113	16	146/ 74	No	Yes
6	53	230/130 to 220/106	224/113	7	210/120	Yes	No
7	55	180/105 to 158/ 95	174/102	12	115/ 80	No	Yes
8	56	220/130 to 190/100	207/110	8	158/ 90	Yes	Died*
9	40	225/130 to 204/100	237/112	13	204/ 88	Yes	Died*
10	63	210/146 to 190/128	202/133	5	140/ 80	Yes	Yes
11	50	250/155 to 216/120	230/130	18	180/100	No	No
12	50	230/130 to 186/100	205/110	47	190/120	Yes	No
13	63	240/168 to 190/128	215/145	31	138/ 70	No	Yes
14	52	228/138 to 208/104	221/122	8	182/ 90	No	No
15	55	250/140 to 198/120	227/137	12	180/100	No	No
16	55	250/140 to 180/ 98	200/110	105	210/114	Yes	No
17	49	260/140 to 190/ 96	204/114	25	180/ 98	No	No
18	43	198/132 to 170/112	181/126	14	148/ 86	No	Yes
19	46	200/100 to 185/ 95	187/109	36	162/ 92	No	No
20	48	208/118 to 178/108	195/115	13	186/ 98	No	No
21	44	168/114 to 154/ 92	159/103	9	162/ 90	Yes	No
22	54	264/132 to 240/120	253/128	9	164/ 84	Yes	Yes
23	51	182/120 to 162/ 98	173/ 98	19	140/ 88	No	No
24	48	198/160 to 184/ 98	200/119	17	184/ 96	No	No
25	51	250/138 to 192/118	221/124	11	196/110	No	No

*Death was due to thiocyanate intoxication.

above 165 systolic and 100 diastolic. In order to adhere to our strict standard of criteria for effect, all these instances, because of the difficulty of their interpretation, were considered ineffective. Table III shows the effect of thiocyanate on the hypertension of chronic diffuse glomerulonephritis. In this group, care was taken not to include patients during an acute exacerbation because of the possibility of an accompanying spontaneous fall of blood pressure as the acute condition subsided.

Table IV represents follow-up observations on fourteen patients in whom the blood pressure was effectively lowered by thiocyanate, and the duration of the hypotensive effect after discontinuance of the drug. The hypotensive effect in this group of patients persisted for from 7 to

TABLE III

RESULTS OF TREATMENT WITH THIOCYANATE IN NEPHRITIC (CHRONIC DIFFUSE GLOMERULONEPHRITIS) HYPERTENSION

No.	*Age*	*Blood Pressure Control*		*Control Period, Days*	*Lowest Blood Pressure after Treatment*	*Thiocyanate Intoxication*	*Effective in Lowering Blood Pressure*
		Range, Mm. Hg	*Average, Mm. Hg*				
1	21	220/140 to 180/120	196/130	7	114/ 64	No	Yes
2	44	290/180 to 234/156	290/165	9	138/ 95	No	Yes
3	47	248/160 to 202/125	229/141	8	160/100	No	Yes
4	60	210/110 to 176/ 90	195/ 98	150	194/ 86	No	No
5	60	210/110 to 176/ 90	195/ 95	143	170/ 86	No	No

110 days, at which time the blood pressure had returned to, or nearly to, its control level. There seemed to be no constant relationship between the persistence of the artificially lowered blood pressure and the amount of thiocyanate required to produce the lowering.

Table V indicates that the effect of thiocyanate cannot be logically anticipated from the average daily dose or the duration of medication. It will be seen that a "trial" was considered completed when the blood pressure fell in accordance with our stated criterion; when toxic symptoms occurred; or when the total amount of thiocyanate administered was in most instances distinctly greater than the amount usually recommended by others as therapeutically effective.

In Table VI, the data of the preceding table are condensed and summarized. They represent an evaluation of the clinical usefulness of various dosages of thiocyanate. The absence of therapeutic effect with 0.163 gm. (2½ grains) daily administered from 77 to 148 days in four patients seemed sufficient reason for considering it an ineffective dosage. The great frequency of toxic manifestations with from 0.978 to 1.62 gm. (from 15 to 25 grains) given daily in ten trials was sufficient evidence for considering this dosage harmful. The dosage of from 0.489 to 0.815 gm. daily (from 7½ to 12½ grains) was accompanied by toxic manifestations in the same percentage as it produced satisfactory lowering of the blood pressure. Moreover, two fatalities occurred in this group as a result of thiocyanate poisoning. The highest percentage of effectiveness with the lowest incidence of toxicity was observed in those patients who received 0.326 gm. (5 grains) daily.

TABLE IV

PERSISTENCE OF HYPOTENSIVE EFFECT OF THIOCYANATE

Number Ambulatory group	*Type of Hypertension*	*Average Daily Dose, Gm.*	*Total Dose, Gm.*	*Persistence, Days*
1	Essential	0.326	8.48	28
2	Essential	0.326	10.76	26
3	Essential	0.652	13.69	49
4	Essential	0.326	15.98	34
5	Essential	0.326	29.35	110
6	Essential	0.489	31.96	55
7	Essential	0.326	33.66	48+
8	Essential	0.489	75.50	41
Hospitalized group				
9	Essential	0.326	4.56	28+
10	Essential	0.652	8.48	15+
11	Nephritic	0.652	9.29	14
12	Nephritic	0.978	10.43	73+
13	Essential	1.192	26.35	7
14	Essential	0.613	31.14	32

The data in Table VII indicate the relative excretion rate of thiocyanate in patients with essential hypertension and in patients with the hypertension of chronic diffuse glomerulonephritis. Furthermore, when the same amount of thiocyanate was administered in a single dose to a "normal" person and one with chronic diffuse glomerulonephritis, the "normal" person excreted an average daily amount twice as great as did the patient with nephritis. It would seem from these observations that the ease with which thiocyanate is excreted bears a direct relationship to the functional integrity of the kidney. Likewise, there appears to be a distinct lack of relationship between the average amount excreted per day and the average amount administered per day. The slow excretion rate of thiocyanate in the presence of glomerulonephritis is reflected in the prolongation of its time for complete excretion as compared with a "normal" person. This is shown in Table VIII. The remaining data in this same table clearly indicate that the days necessary for complete excretion of the drug are roughly proportional to the total amount administered. The observation that at least 4 days are necessary for the complete excretion of a single dose as small as 0.163 gm. (2½ grains), in persons with normal renal function, is striking evidence of the great ease with which thiocyanate accumulates in the body on continuous administration over a period of time.

TABLE V

RELATION OF THE DOSAGE OF THIOCYANATE TO THE EFFECT ON BLOOD PRESSURE AND THE OCCURRENCE OF TOXIC MANIFESTATIONS

No.	*Type of Hypertension*	*Blood Pressure Lowered to or Below 165/100, mm. Hg.*	*Average Daily Dose, Gm.*	*Duration of Medication, Days*	*Total Dose, Gm.*	*Toxic Effect*
1	Essential	Yes	0.326	14	4.56	No
2	Essential	Yes	0.652	7	4.56	No
3	Essential	Yes	0.326	14	4.56	No
4	Essential	No	0.326	18	5.87	No
5	Essential	No	0.652	9	5.87	Psychosis
6	Essential	No	0.978	7	6.85	No
7	Essential	No	0.326	25	8.15	No
8	Essential	No	0.815	10	8.15	Nausea, vomiting
9	Essential	Yes	0.326	27	8.80	No
10	Essential	No	0.326	28	9.13	No
11	Essential	No	0.652	14	9.13	No
12	Essential	Yes	0.326	28	9.13	Psychosis
13	Essential	Yes	0.978	10	9.78	No
14	Essential	No	0.652	15	9.78	Death*
15	Essential	No	0.326	33	10.76	No
16	Essential	No	0.405	28	11.34	Fatigue
17	Essential	No	1.620	7	11.34	Psychosis
18	Essential	Yes	0.326	35	11.41	No
19	Essential	No	0.326	35	11.41	No
20	Essential	No	0.326	35	11.41	No
21	Essential	No	0.170	69	11.73	Dermatitis
22	Essential	No	0.978	12	11.74	No
23	Essential	No	0.978	12	11.74	No
24	Essential	No	0.163	77	12.55	No
25	Essential	No	0.978	13	12.71	Psychosis
26	Essential	No	0.326	40	13.04	No
27	Essential	No	0.652	20	13.04	No
28	Essential	No	0.326	40	13.04	No
29	Essential	Yes	0.691	19	13.13	No
30	Essential	No	0.326	42	13.69	No
31	Essential	Yes	0.652	21	13.69	No
32	Essential	No	0.326	42	13.69	No
33	Essential	No	0.326	42	13.69	No
34	Essential	Yes	0.326	43	14.01	Fatigue, nausea
35	Essential	Yes	0.805	18	14.49	Death*
36	Essential	No	0.326	49	15.97	No
37	Essential	Yes	0.326	49	15.97	No
38	Essential	No	0.489	35	17.11	Fatigue, nausea
39	Essential	No	0.326	55	17.93	No
40	Essential	No	0.652	28	18.26	No
41	Essential	No	0.652	28	18.26	No
42	Essential	No	0.163	121	19.72	No
43	Essential	No	0.326	63	20.54	No
44	Essential	Yes	0.326	66	21.51	No
45	Essential	Yes	0.326	69	22.49	No
46	Essential	Yes	0.326	70	22.82	No
47	Essential	No	0.326	71	23.15	No
48	Essential	No	0.163	148	24.12	No

[*Continued on p. 323*]

TABLE V—(*Continued*)

No.	*Type of Hypertension*	*Blood Pressure Lowered to or Below 165/100, mm. Hg.*	*Average Daily Dose, Gm.*	*Duration of Medication, Days*	*Total Dose, Gm.*	*Toxic Effect*
49	Essential	No	0.326	75	24.45	No
50	Essential	No	0.326	77	25.10	No
51	Essential	No	0.326	77	25.10	No
52	Essential	Yes	0.326	78	25.42	No
53	Essential	No	0.489	52	25.43	No
54	Essential	No	0.648	41	26.57	No
55	Essential	Yes	1.210	22	26.62	Psychosis
56	Essential	No	0.652	41	26.73	No
57	Essential	No	0.652	42	27.38	No
58	Essential	No	0.326	84	27.38	No
59	Essential	No	0.652	42	27.38	No
60	Essential	No	0.652	49	31.95	No
61	Essential	Yes	0.638	51	32.54	Psychosis
62	Essential	No	0.652	50	32.60	No
63	Essential	Yes	0 978	35	34.27	No
64	Essential	Yes	0.652	55	35.86	No
65	Essential	No	0.652	55	35.86	No
66	Essential	No	0.578	78	45.08	No
67	Essential	No	0.652	74	48.25	No
68	Essential	No	0.652	100	65.20	No
69	Essential	No	0.326	203	66.18	No
70	Glomerulonephritis	Yes	0.326	19	6.19	No
71	Glomerulonephritis	Yes	0.978	10	9.78	No
72	Glomerulonephritis	Yes	1.080	10	10.80	No
73	Glomerulonephritis	No	0.326	64	20.86	No
74	Glomerulonephritis	No	0.652	76	49.55	No
1	Normal blood pressure	Yes**	0.652	5	3.26	No
2	Normal blood pressure	Yes**	0.326	14	4.56	No
3	Normal blood pressure	Yes**	0.978	5	4.89	No
4	Normal blood pressure	Yes**	0.326	36	11.74	No

* Death due to thiocyanate intoxication.
** The fall after treatment with thiocyanate was unequivocal and persistent for from two to ten days.

Table IX is a summary of the results of thiocyanate administration in the entire group studied. The blood pressure was effectively lowered in 31 per cent of the hypertensive subjects studied. Almost invariably, a fall in blood pressure was accompanied by subjective improvement. However, subjective improvement occurred in many patients on thiocyanate therapy in whom no lowering of blood pressure occurred. This led us to believe that such improvement was largely psychic.

Furthermore, there is no constant dosage at which either a toxic or a therapeutic effect may be anticipated. Some of the inconstancies

TABLE VI

EFFECTIVENESS OF THIOCYANATE WITH VARIOUS DAILY DOSAGES

Daily Dose, Gm.	*Number of Trials*	*Blood Pressure Lowered to or Below 165/100 mm. Hg.*	*Effectiveness, Per Cent*	*Number of Toxic Cases*	*Thiocyanate Intoxication, Per Cent*	*Number of Fatal Cases Due to Thiocyanate Intoxication*
0.163 (2½ grains)	4	0	0	1*	25	0
0.326 (5 grains)	34	12	35.2	3	8.8	0
0.489-0.815 (7.5-12.5 grains)	26	6	23	6	23	2
0.978-1.63 (15-25 grains)	10	5	50	3	33.3	0

* Maculopapular dermatitis.

TABLE VII

A COMPARISON OF THE EXCRETION RATE OF THIOCYANATE IN ESSENTIAL HYPERTENSION AND NEPHRITIC HYPERTENSION*

No.	*Type of Hypertension*	*Average Daily Dose, Gm.*	*Average Thiocyanate Excretion, Gm. per 24 Hr.*
1	Nephritic	0.978	0.097
2	Nephritic	1.004	0.277
3	Nephritic	0.652	0.250
4	Essential	0.978	0.540
5	Essential	0.915	0.557
1	Normal	1.143 (single dose)	0.088
2	Nephritic	1.143 (single dose)	0.043

* Chronic diffuse glomerulonephritis.

observed are illustrated by the following observations: One patient who responded, by a fall in blood pressure, to 0.326 gm. (5 grains) daily on three successive occasions failed subsequently to respond to a repetition of treatment with the same dosage over a similar period of time. Another patient who responded, by a satisfactory fall in blood pressure, to 0.326 gm. (5 grains) given daily on two different occasions failed subsequently to respond to 0.652 gm. (10 grains) daily given over a

TABLE VIII

EXCRETION TIME OF THIOCYANATE (SINGLE DOSE)

Diagnosis	*One Dose, Gm.*	*Days Necessary for Complete Excretion*
Normal*	0.163	5
Normal	0.163	4
Normal	0.163	4
Normal	0.163	4
Normal	0.326	9
Normal	0.652	11
Normal	1.143	14
Nephritis**	1.143	22

* No evidence of organic disease.
** Chronic diffuse glomerulonephritis.

TABLE IX

SUMMARY OF RESULTS OF TREATMENT WITH THIOCYANATE

	Number of Trials	*Blood Pressure Lowered to or Below 165/100, mm. Hg.*	*Effectiveness in Lowering Blood Pressure, Per Cent*	*Toxic*	*Deaths Due to Thiocyanate Intoxication*
Normal	4	4	100	0	0
Essential hypertension	69	20	28.9	13	2
Nephritic hypertension	5	3	60	0	0
Hypertension, total	74	23	31	13	2

comparable period of time. A third patient who responded satisfactorily after a total dose of 13.2 gm. (202 grains) subsequently became severely toxic (hallucinations of sight and hearing, disorientation, etc.) on a total dose of 12.74 gm. (195 grains).

This uncertainty regarding proper dosage, coupled with the fact that frequently there is slight if any difference between the amounts that produce therapeutic and toxic effects, lead us to believe that thiocyanate has no place in the rational treatment of hypertension.

TABLE X

AMOUNT OF THIOCYANATE IN THE BODY AT THE TIME OF THE FIRST DEFINITE FALL IN BLOOD PRESSURE AND AT THE TIME OF THE FIRST SIGN OF INTOXICATION

	Dosage, Gm.		*Residual Drug at First Fall in Blood Pressure, Gm.*	*Residual Drug at Thiocyanate Intoxication, Gm.*	*Average Daily Thiocyanate Output in Urine, Gm.*
	Total	*Average Daily*			
Nephritic*	9.78	0.978	8.96	....	0.097
Nephritic*	10.80	1.080	9.03	....	0.275
Essential hypertension	9.78	0.652	....	8.49 (died)	0.086
Essential hypertension	12.71	0.978	....	5.00	0.536
Essential hypertension	8.15	0.815	....	5.73	0.213
Essential hypertension	9.78	0.978	8.09	....	0.192
Essential hypertension	5.87	0.652	....	3.22	0.151
Essential hypertension	26.62	1.210	20.88	21.56	0.262
Normal	4.89	0.978	2.29	....	0.339
Normal	4.56	0.326	2.89	....	....
Normal	3.26	0.652	2.90	....	0.115

* Associated with diffuse glomerulonephritis.

TABLE XI

FREQUENCY OF OCCURRENCE OF TOXIC MANIFESTATIONS IN 74 SUBJECTS

Toxic Manifestations	*Frequency of Occurrence*
Nausea	8
Muscular fatigue	7
Vomiting	7
Mental confusion and disorientation	7
Hallucinations of sight and hearing	6
Motor aphasia	3
Death	2
Dermatitis	1

This attitude was widely accepted and thiocyanate therapy in hypertension was almost completely abandoned. However, there has been a recent revival of interest principally based upon studies by Barker.[3] He has indicated that repeated estimations of the blood thiocyanate concentration would serve to prevent overdosage, i.e., if the blood concentration were maintained between 6 and 12 mg. per cent, toxic effects were not likely to occur. In his series of forty-five patients no toxic effects appeared in those subjects whose blood concentration of thiocyanate was 15 mg. per cent or less.

Dr. Chasis and I had previously considered the relationship between dosage and toxic effects. However, instead of blood concentration we determined the residual drug in the body each day by subtracting the amount excreted from the amount administered. By this means we were in a position to know how much thiocyanate was retained in all body tissues and not only that in the circulating blood. Moreover, the estimation of residual drug is not subject to the fluctuation inherent in estimations of blood concentration which is in part influenced by variations in total circulating volume.

In order to determine the relationship, if any, between residual drug and the first evidence of its so-called therapeutic or toxic effect, a group was selected for study consisting of three persons with normal blood pressure, six with essential hypertension and two with hypertension associated with chronic diffuse glomerulonephritis. The results of these observations are shown in Table X. There can be little doubt from the observations presented that toxic effects and even a fatal outcome may occur in some patients who have in their tissues a smaller amount of thiocyanate than others who, not only do not become toxic, but experience a satisfactory fall in blood pressure.

Of the fifty patients with hypertension in this series treated seventy-four different times with thiocyanate, thirteen presented toxic manifestations. In eleven of these the toxic manifestations disappeared within a few hours to 4 days after discontinuance of the drug. The usual order in which the toxic symptoms made their appearance was as follows: muscular fatigue accompanied or followed by nausea; vomiting; disorientation and mental confusion; motor aphasia; hallucinations of sight and hearing; and, in the fatal cases, progression to delirium, convulsive twitchings, coma and death. The frequency with which these toxic manifestations were observed is shown in Table XI. It is noteworthy

that while ambulatory patients who become toxic notice muscle fatigue as the first indication, this symptom may pass entirely unnoticed in patients confined to bed, in whom it is not unusual for motor aphasia, mental confusion or even hallucinations to be the first sign of thiocyanate intoxication.

The remaining two patients who became toxic died of thiocyanate poisoning.

The first fatal case was that of a patient M., aged 40. Her hypertension was of the essential type. The duration of her hypertension was not known. Three months before admission to the hospital she developed a severe occipital headache, which was continuous, and dimness of vision. Her blood pressure during the control period, ranged between 255 systolic and 130 diastolic and 204 systolic and 100 diastolic. The fundi showed the changes of malignant hypertensive neuroretinitis. The concentration test showed a fixation of specific gravity between 1.008 and 1.014. The red blood cells numbered 4,000,000 and the hemoglobin content was 50 per cent. The urine was negative for albumin and blood. On the thirteenth day after admission thiocyanate was begun in dosage of 0.652 gm. daily. On the fourteenth day, after 9.12 gm. had been given, the patient complained of nausea and the blood pressure was 186 systolic and 96 diastolic. On the following day nausea was more marked, but the blood pressure had risen to 220 systolic and 110 diastolic, so that another dose of 0.652 gm. was given. Later on in this day she became somewhat confused and incoherent. Thiocyanate was discontinued. A total of 9.77 gm. had been given in 15 days. The blood pressure continued high, and on the following day she became violently delirious with hallucinations of sight and hearing, extreme motor restlessness, nystagmus and frequent convulsive movements of the extremities. She was completely disorientated, continually muttering and thrashing about so violently as to require mechanical restraint. During the last 24 hours she voided almost no urine and was markedly dehydrated in spite of repeated saline hypodermoclyses and dextrose infusions. The stuporous state became more profound, and death occurred 66 hours after thiocyanate had been discontinued. On the day of death, the blood pressure was 212 systolic and 106 diastolic. Seven days before the end the nonprotein nitrogen content of the blood was 33 mg. per hundred cubic centimeters. Two days before the end the nonprotein nitrogen content was still within the normal range, being 45 mg., and the creatin-

TABLE XII

ANALYSIS OF TISSUES FOR THIOCYANATE CONTENT

Tissue	*Estimation of Thiocyanate Content of Tissues of a Patient in Whom the Drug Proved Fatal,* Mg. per 100 Cc.*	*Estimation of Thiocyanate Content of Tissues of a Patient to Whom no Thiocyanate was Given, Mg. per 100 Cc.*
Heart	9.7	.....
Kidney	15.4	Trace
Spleen	9.2	Trace
Liver	14.5	4.0
Lung	17.0	None
Bone	None	None
Brain	8.0	None

* Patient M. (see text).

ine 2.4 mg. per hundred cubic centimeters. On the same day the urea clearance showed 41.2 per cent of normal function for the first hour and 34.8 per cent for the second hour. At the time of onset of the toxic symptoms, 1.29 gm. of thiocyanate had been recovered in the urine, leaving a residual of 8.49 gm. A necropsy was performed. The anatomic findings were: lungs, congestion; heart, pericardial effusion, hypertrophy, inactive mitral stenosis and subendocardial hemorrhages; atheroma and ulceration in the abdominal aorta; kidneys, nephrosclerosis with profound arteriolar sclerosis, but no necrotizing lesions, and predominantly normal glomeruli; brain, edema.

The fresh tissues were analyzed for thiocyanate content. Table XII indicates the results of the analysis as compared with the tissue content in a patient who had not received the drug during life. These analyses were made by Dr. Kenneth Blanchard of the department of biology, New York University.

The second fatal case was that of a patient Mc., a woman, aged 56. Her hypertension was of the essential type. During the control period her blood pressure ranged from 220 systolic and 130 diastolic to 190 systolic and 100 diastolic. After receiving a total of 14.49 gm. in 18 days, an average daily dose of 0.805 gm., she complained of nausea. The thiocyanate was immediately discontinued. There had been no

appreciable fall in blood pressure. Forty-eight hours after the drug had been discontinued she developed nervous manifestations almost identical with those described in patient M. She persisted in this state for 6 days and died. Necropsy was not permitted.

In an attempt to explain the occurrence of toxic phenomena, one is first concerned with the dosage used. It might be expected that toxic manifestations would occur only when the larger dosages were given. That this is not so in the case of thiocyanate is clear from Table X. Severe toxic manifestations occurred in some patients who had received less of the drug, both in total and average daily dosage, than others who developed no toxic signs.

It further appears from our observations that in certain persons there is little or no margin of safety between the toxic and so-called therapeutically effective dose of thiocyanate.

We are of the opinion, therefore, that thiocyanate should not be administered to hypertensive patients for the purpose of lowering blood pressure, because, apart from its toxic effects, its influence is not striking in either the frequency or the extent of blood pressure reduction; that almost any medical or psychotherapeutic measure may be expected to yield results equally effective and with no element of danger.

What might be called the modern period of therapy began in 1923 with Daniélopolu.[4] In 1875 Gull and Sutton published their report on arteriocapillary fibrosis. It was their opinion that widespread arteriolar sclerosis in the splanchnic area occurs first, and the obstruction to blood flow mechanically results in an increase in blood pressure.

Some years later Huchard[5] and Allbutt[6] took the opposing view. They noted, in independent investigation, that persons dying with hypertension might at necropsy show no significant arteriolar sclerosis. They concluded therefore that hypertension was the clinical expression of splanchnic functional vasoconstriction and that the arteriolar sclerosis was secondary to the elevated blood pressure.

Daniélopolu[4] in common with most students of hypertension accepted this view. Since it was known that the sympathetic nerves carry vasoconstrictor fibers and since the splanchnic area is the largest vascular bed whose sympathetic nerve supply is accessible, he suggested and carried out the first sympathectomy for the treatment of essential hypertension.

In 1925 Adson[7] stimulated interest in this operative procedure in

this country. At first the reports were highly enthusiastic. The first intimation that the results were not uniformly encouraging was the introduction of modifications of the operative procedure such as resection above the diaphragm, below the diaphragm, with and without partial resection of the adrenals and the celiac ganglion, and anterior nerve root section. Finally, Smithwick has introduced an extension of the technique for splanchnicectomy and sympathetic ganglionectomy.

As time went on, enthusiasm waned to the point now where applicants for this type of surgery are generally discouraged. As time goes on, more and more of those whose blood pressure had temporarily fallen have returned to their previous hypertensive levels. The one striking benefit has been the relief of incapacitating headache. Indeed, there are those who feel that even this and nothing more is full justification for the operative procedure in those in whom frequent paroxysms of headache have become intolerable.

Rytand[8] studied forty patients before and after sympathetic surgery to evaluate if possible the subjective and objective benefits to be derived from this procedure. His conclusions reflect widespread present feeling, and are worth repeating:

"In general the results were poor. In only one patient was there a brilliant result, although in five others there was some degree of success in reducing blood pressure. Six more patients felt better, but their arterial pressures were not lowered. In nine patients there was no change. Eleven died within a year and a half, with their condition unchanged (transient relief of symptoms occurring in five of these). Eight died within two weeks of the operation. From a consideration of what is known about the pathologic physiology of arterial hypertension and the effects of denervation it would seem that not much could be expected from any such denervating operations."

In considering the rationale concerned with sympathetic surgery in hypertension you will remember that the first suggestion had to do with the observation that essential hypertension is a functional vasoconstrictive disease; that the vasoconstriction is principally confined to the splanchnic area; and that section of the splanchnic vasconstrictor nerve fibers might be expected to remove, if not the cause, certainly the anatomical pathway through which the cause becomes effective. It remained for Prinzmetal[9] and Pickering,[10] working independently, to cast doubt upon the validity of some of these assumptions. Prinzmetal[9]

makes the following pertinent observations:

"1. Determinations of resting blood flow in the arm in hypertension give an average value no greater than that obtained from subjects with normal blood pressure. This indicates that increased vascular resistance in hypertension is not confined to the splanchnic area but generalized throughout the systemic circulation.

"2. Anesthetization with novocain of the vasomotor nerves to the arm produces the same increase in flow in normal subjects and patients with hypertension, proving that the vascular hypertonus is independent of the vasomotor nerves, and that this hypertonus must therefore be regarded as intrinsic spasm of the blood vessels themselves.

"3. Surgical procedures aiming at the relief of high blood pressure by sympathectomy do not abolish the vascular hypertonus which is fundamentally responsible for the hypertension."

Increased blood pressure is one of the symptoms of hypertensive disease. It is influenced by many variables, some known and, very likely, some unknown. Since one of the known influences on blood pressure is sympathetic vasoconstriction, it is not surprising that widespread interruption of these impulses results in lowered blood pressure in some patients. It is reasonable to expect that the most marked postoperative falls in blood pressure will occur in those patients in whom extrinsic vasoconstriction contributes in greater part to the increased peripheral resistance. It is likely that the occasional so-called brilliant result is seen in patients in this category. Unfortunately, there is no unequivocal means of preoperative recognition of this more favorable group. In no sense, however, can sympathectomy be regarded as a cure of hypertensive disease. It does not remove the ultimate cause, but merely interrupts the pathway through which the cause is effective in producing one symptom of the disease, i.e., increased blood pressure, and even this effect, while undoubtedly beneficial, is not common and often temporary.

We now come to the present phase in the treatment of essential hypertension which is presumably based upon knowledge of the mechanism involved. This present phase of therapy was evolved entirely from observations on experimental hypertension in the animal. In 1933 Goldblatt and his associates demonstrated for the first time that persistent elevation of systolic and diastolic blood pressures could be induced in the animal by partial constriction of both main renal arteries.

Since this observation there have been many advocates of the thesis that human essential hypertension is on this same basis, namely, renal ischemia.

The observations which tend to support this simplified concept of hypertension in man would be acceptable in a given patient if:

1. Renal ischemia can be demonstrated to have preceded the hypertension.

2. Abolition of renal ischemia results in return of blood pressure to normal.

The first provision has not been established in man. The occasional observation in man of renal artery placques associated with hypertension is presumptive evidence only. As has been pointed out by Oppenheimer, Klemperer and Moschkowitz,[11] it is just as reasonable to assume that the placque results from the hypertension as to assume that it leads to the hypertension. In the aged, where decrescent arteriosclerosis results in large wedgeshaped ischemic areas in the kidneys, diastolic hypertension does not occur. Furthermore, measurement of the rate of renal blood flow, the essential measurement in the critical examination of this question, is now possible. Not only are we in a position to measure the rate of renal blood flow, but also the amount of functioning renal tissue. A ratio of these two measurements would indicate the number of cubic centimeters of blood supplied to each unit of functioning renal tissues per minute. With this method, ischemia can be defined quantitatively and accurately measured. By means of this method the relationship between renal ischemia and hypertension can be more fully examined.

Drs. Chasis, Ranges, Bradley and I,[12] of the Department of Medicine, working with Dr. Homer W. Smith, Professor of Physiology at the New York University Medical College, have examined a group of patients with essential hypertension with these methods. We found that the hypertensive kidneys showed a diminished blood flow per unit of functioning renal tissue as compared with the normal kidney. However, it was concluded that the renal ischemia was a result of the hypertension and not its cause. This conclusion seemed amply substantiated by the observation that renal ischemia and hypertension could be produced in a normal subject by the administration of epinephrin or angiotonin; furthermore, in hypertensive subjects the renal ischemia is reversible under the influence of the pyrogenic reaction induced by foreign pro-

tein injection. One way to examine critically the relationship between the renal ischemia and elevated blood pressure would be to dispel the renal ischemia and note the effect on blood pressure. At the present this procedure cannot be applied to answer the question since the pyrogenic reaction employed to induce renal hyperemia so alters systemic hemodynamics as to make interpretation impossible.

Doctors Wellen, Welsh and Taylor[13] of the Department of Obstetrics and Gynecology, using these methods, found that in toxemia of pregnancy at the height of the elevated blood pressure, the renal blood flow per unit of functioning renal tissue was normal, i. e., there was no ischemia. This observation is strikingly important to the question under discussion, since late pregnancy would seem to be the ideal situation for the development of hypertension on the basis of renal ischemia. Hypertension in specific toxemia occurs late in pregnancy when the uterus is large, and hydroureter and hydronephrosis due to pressure are common. Furthermore, in the great majority of such women there is a temporary or permanent fall of blood pressure to normal when the uterus is emptied. It would seem from these observations that in spite of the apparent reasonableness of the assumption, the hypertension of specific toxemia of pregnancy is not on the basis of renal ischemia. One might take the attitude that hypertension, like fever, is an expression of many causes and that renal ischemia might serve as the basis for the hypertension in a small number of patients. If this is true, therapy can be possible of success only if the hypertension in question is on a renal ischemic basis. Such therapy might be medical, as suggested by the present attempts with antipressor renal extracts, or surgical, by removal of a single diseased kidney, or a surgical procedure designed to increase the effective blood flow to the ischemic kidneys. Unfortunately, no distinction can be made now between human hypertension on a renal ischemic basis and hypertension on some other basis. There is one possible exception and that concerns the unilateral ischemic kidney. Drs. Chasis and Redish[14] have made measurements of renal blood flow and renal mass for the detection of renal ischemia on each kidney separately, by means of ureteral catheterization. They have been good enough to allow me to use briefly one of their subjects. This Figure 1 shows ptosis and hydronephrosis of the right kidney. The patient has marked elevation of blood pressure. The only point I wish to make is that the renal blood flow and functioning renal mass are identical on both sides.

Fig. 1—Retrograde pyelogram (erect position, anterior-posterior) showing angulation of right ureter with moderate hydronephrosis.

In other words, the apparently damaged kidney is not ischemic relative to the apparently normal kidney. Nephrectomy or any other surgical measure applied to the ptosed kidney for the treatment of the hypertension, would have been unwarranted.

The role of the kidney in the pathogenesis of hypertension and therefore the specificity of unilateral nephrectomy in its cure has been fully established for experimental renal ischemic hypertension in the animal. Whether or not this relationship obtains in man is still open to question.

A few highly enthusiastic reports suggest that occasionally a unilateral destructive renal lesion, such as congenital aplasia or atrophic pyelonephritis, may initiate the hypertensive process. Dr. Chasis and I have reviewed in detail every case report in the literature in which unilateral nephrectomy was performed for the cure of hypertension, or in which renal pathology in a hypertensive patient was indication for the nephrectomy; seventy-five such case reports have appeared in the litera-

ture to date. We regarded as acceptable demonstration of the beneficial effect of nephrectomy in hypertension, those patients in whom hypertension was established by adequate preoperative control and whose blood pressures fell to normal soon after nephrectomy and persisted in the normal range of at least one year. Of the seventy-five recorded cases, only eight fulfilled these criteria. Even this small apparently-successful group is not final proof that unilateral nephrectomy can cure hypertension, because high blood pressure may subside for long periods of time as a result of the non-specific effects of any surgical procedure.

The assumption in unilateral nephrectomy for the cure of hypertension, is that removal of an ischemic kidney eliminates the source of the pressor agent. When the blood pressure does not return to normal, it is assumed that the remaining kidney is ischemic, either as a result of unrecognized intrinsic disease or because of arteriolar sclerosis secondary to the preëxisting hypertension. I shall cite one patient in whom hypertension persisted in spite of complete abolition of renal ischemia. A 45-year-old white female was referred to Dr. Chasis by Dr. Edward Weiss, of Philadelphia. Measurements of blood flow and amount of functioning tissue were made on each kidney separately. In the right kidney the blood flow-tubular mass ratio (CD/TMD) was 8, indicating well marked ischemia, and in the left kidney there was practically no measurable blood flow or functioning renal tissue. The left kidney was removed and showed atrophic pyelonephritis. One month after nephrectomy Dr. Chasis repeated the measurements on the remaining right kidney and found a blood flow-tubular mass ratio of 12.2, which indicated a normal amount of blood reaching each unit of functioning tubular tissue, i.e., no ischemia. In spite of the complete elimination of renal ischemia the blood pressure level was unchanged and remained definitely elevated. The evidence presented throws considerable doubt on the concept of unilateral ischemic hypertension in man and consequently on the rationale of nephrectomy for its cure. Before closing this phase of the subject let me say that we believe it entirely logical that partial obstruction of one or both main renal arteries is capable of producing hypertension in man as in the experimental animal. This is well demonstrated by the published case of Leadbetter and Burkland. Their patient was cured during a 3-year follow-up period after removal of a kidney whose main renal artery was partly obstructed by a congenital muscle tumor. Their experience is unique and the only reported

instance of its kind. In our opinion it is not analogous to the far more common association of unilateral intrinsic renal disease and hypertension in which we believe the renal disease and hypertension are not related.

In accordance with the assumption that hypertension in man is initiated by renal ischemia, two other operative procedures have been suggested and tried. Renal-omentopexy to supply a new source of blood to the kidneys and nephropexy to correct interference with renal blood flow presumably due to ptosis of the kidney with kinking of the ureter.

Unilateral renal-omentopexy was performed on two patients at Bellevue Hospital, by Dr. Arthur Wright. The functional measurements, made up to 18 months after operation, indicated that blood flow to the operated kidney was actually decreased by a surgical procedure designed to do the opposite.

In another patient with marked nephroptosis, nephropexy was performed by Dr. Howard Jeck. Again the measurements made 12 months postoperatively showed a diminution of blood flow in the operated kidney. In neither of these patients was the blood pressure lowered.

At the present time considerable interest is centered on two nonsurgical measures designed to reduce high blood pressure, both presumably directed toward the initiating mechanism. One is concerned with the antipressor effect of renal extract and the other with completing the process of deamination.

Treatment with a renal extract has its basis in a number of experimental observations which suggest that normal renal tissue contains a substance capable of opposing the pressor action of angiotonin or similar pressor substance liberated from an ischemic kidney. It presupposes therefore that essential hypertension in man is initiated by a pressor mechanism originating in a manner analogous to that which obtains in the renal ischemic animal. This material is being administered to patients parenterally by Page and his associates[15] and orally by Grollman and his associates.[16] Both groups have been cautious in their interpretation of the results in man. Page and his associates indicate only that "the extracts may have merit." Extensive clinical trial has been handicapped by the difficulties inherent in the manufacture of an adequate amount of active material. Furthermore, alarming instances of peripheral circulatory collapse have occurred following parenteral administration. Before final estimate is possible, an extract free of impurities will have to be

administered to a larger number of hypertensive subjects. In the light of our own present opinion that there has been no demonstrated analogy between human and experimental hypertension, data on treatment with the extract cannot logically be transferred from animal to man. A further barrier to the acceptance of the specificity of renal extracts is the well-known fact that blood pressure can be lowered by the parenteral administration of any foreign protein. Drs. Chasis and Smith and I[17] have demonstrated this with the administration of typhoid vaccine, intravenously and subcutaneously. The pyrogenic reaction which occurred with each adequate dose was followed by marked temporary fall in blood pressure and on two occasions with falls to shock-like levels, as described with renal extracts by Page and his associates.[15] By daily administration of typhoid vaccine it was possible to maintain a distinctly lowered blood pressure indefinitely. Although premedication with amidopyrine prevented the chill and fever components of the pyrogenic reaction, it was just as effective in lowering the blood pressure. We concluded that this hypotensive effect was due to widespread acute vasodilatation and represented an unphysiological and therefore undesirable effect. It must be emphasized, however, that although renal extracts may owe part of their effect to a non-specific pyrogenic reaction, a specific antipressor action may still be operating.

The second non-surgical and presumably specific therapy is based upon the thesis that ischemic renal tissue is deprived of adequate oxygen. As a consequence amines would not be deaminized, and since they are known to be pressor, their accumulation in the blood would result in hypertension. To correct this metabolic fault it has been suggested that amine oxidase be administered. The observations of Holtz[18] and Bing[19] have established the probable validity of this hypothesis. Schroeder[20] has made observations on man with tyrosinase and Soloway, Oster, Friedman, Marrus and Oppenheimer[21,22] in rats, using certain quinones. The effect on the experimental hypertension of rats, while striking, is subject to the same difficulty of interpretation as with renal extract in the hypertensive dog, i.e., that the mechanisms of human and experimental hypertension have not been shown to be analogous. In attempts to reduce the blood pressure in hypertensive humans with Tyrosinase we encountered the pyrogenic reaction which obscured any specific antipressor effect which may have been concomitantly present. For a final estimate of its value in human hypertension, as with renal extracts,

further trial is necessary with an amine oxidase free of pyrogenic agents, and the observations must be made in man.

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PULMONARY IRRITANTS*

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CLASSIFICATION OF PULMONARY IRRITANTS

PULMONARY irritant or injurant substances comprise a group of compounds that exist as gases, or as liquids that have a sufficiently high vapor pressure under ordinary conditions to give rise to injurious concentrations in respired air.

Of greatest interest among these, for the purposes of the present discussion, are the acid gases—substances that appear to owe their physiological effects to the fact that they are acids or that they behave like acids under the conditions of their use—these being hydrogen chloride, bromide and fluoride, and chlorine, bromine, sulfur dioxide and certain oxides of nitrogen, together with phosgene, diphosgene and chloropicrin. There are other less common members of this group, and there are also non-irritant, unstable alkyl halogen compounds that exert their primary effect upon the nervous system when inhaled, subsequently, and apparently through hydrolysis, yielding substances that act as irritants, inducing extensive circulatory and pulmonary damage. Whether the pulmonary damage in the latter group is due mainly to circulatory failure, or to the exhalation of an irritant decomposition product of the original compound has not been established, but the lung pathology is so like that caused by the inhalation of an irritant gas as to justify the inclusion of these compounds in this group.

Next, come members of the group classified for the purposes of chemical warfare as vesicants. The best known among these, mustard and lewisite, must be regarded as pulmonary irritants in the toxicological sense, since despite their low vapor pressure, they give rise at ordinary temperatures to highly irritant concentrations of vapor. The serious pulmonary injury sustained by persons who inhale these vapors does

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not lend itself to satisfactory explanation, and nothing will be said concerning its pathological physiology in this discussion. The injurious effects of the inhalation of these vapors must be mentioned, however, because of the pattern of the clinical condition that develops—a pattern that is different in many respects from that associated with exposure to the acid gases. These effects will be dealt with briefly at an appropriate time.

Certain other gases, of which ammonia and formaldehyde may be mentioned as examples, do not fit into either of the preceding groups. Inhalation of these substances in sufficiently high concentrations induces the symptoms and the pathologic picture of acute upper respiratory and pulmonary irritation. They are mentioned only to call attention to the fact that this classification of irritant respirable substances is of necessity somewhat incomplete.

Finally, the carbonyls would seem to come within a toxicologic classification of pulmonary irritants, because of their property of depositing finely divided particles of metal in the lung tissue, thereby inducing an intense pulmonary irritation and edema. Iron and nickel carbonyl represent the best known examples of this group. For a variety of reasons these compounds scarcely seem destined to play an important role in chemical warfare, and therefore they are mentioned only as interesting examples of an additional and apparently unique type of pulmonary irritant.

Certain Properties of Pulmonary Irritants

Correlation and comparison of certain of the physical, chemical, and physiological properties of some of the substances referred to in the foregoing paragraphs will serve to illustrate practical points of importance.

Table I calls attention to the importance of volatility in determining the comparative potentialities of compounds that have about the same toxicity (compare mustard and the potentially more dangerous lewisite), while at the same time it shows how unimportant relative volatility may be when a compound is sufficiently toxic (compare chlorine with mustard).

Table II demonstrates how little relationship there may be between the actual toxicity of one of these compounds, and the immediately painful sensation of upper respiratory and pulmonary irritation that

TABLE I

COMPARISON OF VOLATILITY AND LETHAL CONCENTRATION OF IRRITANT AGENTS

	Concentration in milligrams per liter				
	Phosgene	*Chloropicrin*	*Chlorine*	*Mustard*	*Lewisite*
Vapor in air at 20° C	∝ (gas)	∝ (gas)	∝ (gas)	0.57	4.50
Fatal for 30 min. of exposure	0.36	0.80	2.50	0.07	0.05
Fatal for 10 min. of exposure	0.50	2.00	5.60	0.15	0.12

TABLE II

COMPARISON OF MINIMUM DETECTABLE, IRRITATING AND LETHAL CONCENTRATIONS OF IRRITANT AGENTS

	Concentration in milligrams per liter				
	Phosgene	*Chloropicrin*	*Chlorine*	*Mustard*	*Lewisite*
Minimum detectable odor	0.0044	0.007	0.01	0.0013	0.014
Minimum irritating concentration	0.005	0.009	0.029	0.001*	0.008*
Fatal for 10 min. of exposure	0.50	2.00	5.60	0.15	0.12

* There is a latent period before presence is apparent.

result from exposure to it. In practical terms this means that not all of them give adequate warning of their presence in dangerous concentrations in the respired air.

Still other properties of these substances are important factors in their behavior. Their solubility in water, or the avidity of their combination with water, may be the determining factor in the locus of their action. Thus the primary effect of exposure to the highly soluble chlorine, ammonia, and sulfur dioxide is exerted upon the upper respiratory tract, and if one is exposed to low or moderate concentrations for periods that are not too long, the damage done is confined almost entirely to the nose and throat. In contrast, the chief injury associated with the inhalation of correspondingly irritating concentrations of phosgene occurs in the lung.

The General Effects of Exposure to Pulmonary Irritant Gases

Much has been made of the importance of the time-concentration relationship in exposure to noxious gases, and in general emphasis upon this relationship is justified. A certain caution must be exercised against complete reliance upon it. The duration of the exposure to an highly irritant gas is important, but the severity of the effect cannot be expressed as the product of concentration and time, except within certain limits of concentration, because of the disproportionately injurious effects of brief exposures to high concentrations, as well as the negligible effects of sufficiently low concentrations. This can best be appreciated if it is recognized that there are at least four, and perhaps five, types of effect that result from various combinations of concentration and length of the exposure.

1. The effect of exposure to very high concentrations may be virtually immediate anoxic death. Whether this outcome is the result of direct damage to the respiratory membrane rendering it impermeable to the normal respiratory gases, whether it is due to rapid absorption of the poison with central respiratory paralysis, or whether it is due to circulatory collapse (vagus shock), is not apparent. The pathological picture in experimental animals suggests that the last mentioned possibility is the most likely.

2. Another result of brief exposure to high concentrations of these gases, which may differ only in degree from that previously described, is extensive immediate damage to the pulmonary and upper respiratory tissues. Acute hyperemia, hemorrhage and tissue destruction (coagulation necrosis) may be the prominent features of the pathological picture, or alternatively, if death occurs promptly, there may be acute emphysema, general acute interstitial edema, ischemia and coagulation necrosis. In this and in the previously mentioned type direct pulmonary injury is much more prominent than reaction to injury or the secondary effects, chiefly because death occurs before these have time to develop.

3. The third group of effects is that with which we are most concerned in that it offers an opportunity for survival. Here, there is pulmonary injury of a serious type, and accompanied by upper respiratory damage that varies in degree with the nature of the agent and its concentration in the air breathed by the victim. It is to this general set of effects that we shall give detailed consideration.

4. A fourth type of effect is that following exposure to concentrations of noxious substances that are insufficient to cause immediately serious injury to the respiratory tissues, over such a period of time as to cause accumulation of these noxious substances in the tissues of the body as a whole and thereby to induce systemic intoxication. This type of effect is of no practical importance in relation to chemical warfare. It is of some interest, however, to recognize that a dangerous and even lethal dose of an acid gas may be absorbed from the respired air without doing greater damage to the lungs than to the other organs.

5. A still further set of effects is that produced by mild exposures to respiratory irritants for comparatively short periods, following which the injury is limited almost entirely to irritation of the eyes and upper respiratory tract. There is stinging and burning of the eyes, nose, and throat, redness and weeping of the eyes and the respiratory and pharyngeal mucosa, sneezing perhaps and certainly coughing, with a sore throat and huskiness or perhaps loss, of the voice. There may be headache, originating from irritated accessory nasal sinuses. Nosebleed is not infrequent, and there may be some blood-tinged sputum from the pharynx and trachea, but there will be little chest pain except perhaps the muscular soreness associated with excessive coughing. These effects last from a few minutes to several hours, with more prolonged lesser effects, among which the soreness of the throat and the huskiness of the voice may be the most persistent.

The Effects Upon the Respiratory System of Serious Exposure to Irritant Agents

Immediate effects: The initial symptoms of exposure to irritant gases are those of sharp burning pain in the eyes, nose and throat, with constriction of the throat, irregular respiration, followed by rapid, dyspneic respiration, and subsequently by some degree of relief as the secretions of the eyes and nose begin to flow and bathe the irritated surface. The severity of these symptoms varies with the characteristics of the agent involved, and with the concentration to which one is exposed. Labored breathing with spasmodic coughing may be prominent, and chest constriction and pain, with air hunger and the fear of promptly impending death, may develop. Upon escape from exposures of less than extreme severity, there is some degree of relief from the more acute distress, but the coughing continues for some time, producing considerable mucus

which is likely to be blood-tinged and may be frankly hemorrhagic, and the burning of the nose and throat continues. The voice becomes husky and may be reduced to the merest whisper. Gradually some degree of comfort ensues in most cases.

Effects during following twenty-four hours: After two to twelve hours of relative comfort, respiratory distress, accompanied by the increasing physical signs of pulmonary moisture, may begin to develop, and may reach an acute stage promptly, especially if the victim exerts himself in any way. There may be no interval of relief; in such cases the signs of acute respiratory irritation during exposure are followed by steadily increasing signs of pulmonary congestion and edema or hemorrhage. On the other hand, there may be a gradual subsidence of all of the symptoms of upper respiratory and pulmonary irritation, with little or no evidence of pulmonary edema. Exposed persons, kept under observation over a period of twenty-four hours during which pulmonary congestion and edema have failed to appear, may generally be regarded as free of danger. This period of twenty-four hours following the exposure is crucial, and for such a time the patient must be kept quiet and warm, as comfortable and relaxed as possible, and under careful observation. It is probable also that this is the period during which specific measures for the prevention of pulmonary edema will be indicated, if and when such measures can be developed on a sound physiologic rationale.

Subsequent effects: Exposed persons who do not develop evidences of pulmonary edema within the first twenty-four hours will recover promptly and without further incident, as a rule.

Those who develop pulmonary edema may be ill for periods that vary from a few days to many weeks, dependent upon the severity of the injury sustained. Secondary infection resulting from the invasion of the bacterial flora of the nose and throat into the injured tissues may be expected to develop in the individual who survives the acute chemical injury, and infectious tracheitis, bronchitis, bronchopulmonary abscess, and bronchopneumonia are very likely to follow. Death may occur at any of these stages in the process.

Pulmonary Edema

Since the occurrence of pulmonary edema is the outstanding clinical sign that serious damage to the lungs has occurred as the result of ex-

posure, and since the course and the degree of severity of the pulmonary edema are the most decisive factors in the survival or death of the injured person, we are justified in concentrating our chief attention upon its genesis and development.

Onset: As indicated previously, the onset of pulmonary edema following exposure to irritant gases, may be prompt or it may be delayed for as long as twelve hours. In the young and healthy individual, the longer its appearance is delayed the less likely it is to develop. The outlook is uncertain to some degree in the old or in persons who are the victims of chronic respiratory and circulatory diseases, and therefore the effects of exposure on the part of the civilian population cannot be anticipated with complete assurance on the basis of the experience of armed forces in the last war. The latent period between the occurrence of the exposure to irritant gases and the onset of the edema can best be understood by visualizing the effects induced by contact of the irritant agent with the respiratory tissues.

Pathology: The general character of the injurious effect of the pulmonary irritants (omitting any present references to the effects of exposure to mustard and lewisite) as well as the reaction on the part of the tissues to such effects, is the same throughout the respiratory system. The results differ widely, however, because of the differences in the structure and vascularity of the various parts of the system. Cellular edema, coagulation necrosis and disintegration, hyperemia, congestion, transudation, exudation, diapedesis, hemorrhage, focal necrosis, thrombosis and infarction occur in varying proportions at different sites and times, to make up the whole pathological picture.

In the upper respiratory tract there is a general inflammatory reaction with first a serous, and later perhaps, a sero-sanguineous discharge, and still later ulceration, hemorrhage, exudate and fibrin. Plugs of debris may obstruct larger and also smaller air passages. Later, after the development of pulmonary edema, the trachea will be filled with frothy, watery, perhaps sanguineous fluid, and when pneumonia develops, with a purulent or fibrino-purulent exudate.

In the lung similar damage occurs to the bronchioles and alveolae, on a smaller scale. The picture seen at necropsy depends to a very large degree on the time at which death occurs. The damage is likely to be spotty, rather than general, certain areas being preserved from direct injury by reason of bronchiolar spasm, others being atelectatic or em-

physematous, because of complete or partial obstruction with debris. At first, emphysema, petechial hemorrhage, perhaps confluent hemorrhage, and interstitial edema predominate. Later, large and small areas of deeply congested lung tissue may be seen to be heavy, boggy, and dripping with a thin sanguineous fluid. These may become virtually confluent, the entire lung being large and very heavy, with water running from the cut dark red surface, and with frothy islands of fluid appearing from the cut bronchioles when slight pressure is applied. If death has occurred some days after the onset of the edema, there will be areas of pneumonic consolidation. These may be in any stage of development or resolution dependent upon the time interval between the exposure and death. There may be abscesses or gangrene. Still later, pulmonary fibrosis as well as chronic bronchitis and bronchiectasis may be seen.

The pathological findings are by no means limited to the respiratory system. A later discussion of the pathological physiology of pulmonary edema will show that when death occurs during that stage, it is the result of anoxia and circulatory failure. Accordingly the general signs of circulatory collapse, with widely dilated heart (especially the right side), passive congestion, and venous stasis are very prominent. In addition, the lesions of an acute toxic process—edema, hyperemia, petechial hemorrhage, and focal necrosis—will be found to greater or lesser degree in other organs, notably the kidneys, liver, heart muscle and brain. The systemic effects of the absorption of phosgene, for example, may not be ignored, and would not be reduced to secondary importance except for the overwhelmingly dramatic character of the pulmonary pathology. The blood is dark in color, reduced in volume, and very viscid through hemoconcentration. Capillary thromboses may be seen, and thrombi may be found in larger vessels.

Pathological Physiology: The genesis and the development of the pulmonary and systemic picture may be considered sequentially, in terms of the chief effect—that of the production of anoxia. If it be recognized that bodily requirements in way of oxygen may be met in a variety of normal and unusual circumstances through the joint response of the respiratory and circulatory apparatus, the difficulty presented by gross impairment of the respiratory system will become more apparent. The normal respiratory system can increase its capacity for ventilating the blood some twelvefold or more, while the minute-volume of the circulatory flow can rarely be increased to more than ten times its normal

resting level. The type of injury to the respiratory system with which we are concerned here may deprive the organism of any respiratory reserve soon after exposure, and may well progress to a point where respiration is too ineffectual to sustain life. The large air-ways may be partially obstructed, first by muscle spasm and later by debris, fluid, and froth; large numbers of bronchioles and alveolae may be closed off or filled up with debris, exudate, hemorrhage and fluid; the lung volume is further reduced by atelectasis, consolidation, and fluid; the effective respiratory volume is reduced by maintained, shallow respiration on an expanded, emphysematous chest; the diffusion of oxygen through a greatly reduced area of respiratory membrane is still further hindered by an edematous thickening of that membrane; and the utilization of the limited oxygen supply in the blood is lowered by reason of the reduced oxyhemoglobin dissociation occasioned by the low carbon dioxide tension of the peripheral blood. (The decreased carbon dioxide tension is produced by the relative ease of diffusion of carbon dioxide, aided by the overventilation of intact and unobstructed alveolae.) Every mechanism whereby the available oxygen of the blood can normally be increased is impaired, and the result may well be that the maximum respiratory exchange, in so far as this is mediated by the respiratory apparatus alone, may be greatly reduced below the normal resting capacity. The result obviously is anoxia—an anoxia which can be offset by physiological mechanisms and at normal atmospheric conditions only through increased circulatory activity.

It may be worth while at this point to call attention to the fact that pulmonary edema as we are dealing with it here is the exact antithesis of that more commonly seen in the terminal stages of circulatory failure. The latter arises primarily out of circulatory failure and is a sign of impending death; the former is due to direct chemical injury to the lung, the general circulatory system exclusive of the intrinsic pulmonary circulation being essentially intact. The maintenance of an efficient circulation is seen therefore, to be of paramount importance. Unfortunately the intrapulmonary vascular bed will have suffered damage comparable to that sustained by the pulmonary epithelium, and thereby the circulatory system will have been embarrassed at the point at which the gaseous exchange occurs. With the onset of pulmonary edema there comes further embarrassment in that the water and serum loss into the lung tissue concentrates the blood, decreasing its volume and increasing its

viscosity, thereby promoting stasis and capillary thrombosis. All of these factors, in addition to the reduced interchange of respiratory gases incident to the direct pulmonary damage, throw an increased burden upon the heart.

The sequence of the circulatory changes that may be expected to occur merits special attention. The initial response to anoxia is seen in an increase in cardiac rate and output, the heart remaining approximately normal in size, the arterial pressure increasing in both systemic and pulmonary systems, and the venous pressure showing a moderate increase. So long as the tissue anoxia is readily compensated in this manner, no further qualitative change occurs, but as the edema incident to the pulmonary injury increases, anoxia progresses and the cardiac burden increases. The resistance in the pulmonary circuit increases also, and the load on the right heart becomes disproportionately great. As a consequence of this situation, the right heart increases in volume while the left decreases, the systemic arterial pressure—especially the diastolic—continues to increase, the pressure in the pulmonary artery is still further increased, the venous pressure mounts to high and yet higher levels, the pulse rate increases, and the minute-volume cardiac output decreases to something less than its maximum. At this time there will be capillary dilatation due to the high capillary and venous pressure, and perhaps to some elevation of the carbon dioxide tension, the skin being warm and florid or purplish (cyanosis) in color.

If now the pulmonary edema does not progress, the circulatory system may be capable of maintaining its load successfully, and with the onset of the healing process, survival and recovery may result. If the injury has been sufficiently severe, however, or if the heart begins to fail, the picture changes gradually or perhaps suddenly. The most striking features of the change are dilatation of the right heart, a drop in the venous pressure, a drop in the systemic arterial pressure, the development of a rapid, thready pulse, and the appearance of a grayish, perhaps slightly bluish pallor, with coldness and clamminess of the skin, especially of the extremities.

Clinical Types: An adequate discussion of the variations in the clinical picture that result from exposure to different agents would require much more precise information than is available from industrial experience, from the clinical observations of the First World War, and from animal experimentation. Some few comments may be warranted for

their practical usefulness. Comparison of chlorine, phosgene, and chloropicrin, mustard and lewisite reveal a number of distinct differences.

Exposure to effective concentrations of chlorine results in acute painful injury to the upper respiratory tract, together with somewhat less serious damage to the lungs. Pulmonary edema develops with little or no delay, and reaches its climax within twelve to twenty-four hours. Delayed deaths may result from secondary infection, but apparently not because of general or localized toxic effects in the viscera.

Exposure to phosgene causes little upper respiratory injury or discomfort, and there is a latent period of apparent comfort before pulmonary edema develops. The edema develops rapidly, however, after the onset, most of the deaths occurring within the first twenty-four to forty-eight hours. Delayed deaths occur as the result of pneumonia and also because of toxic damage to the heart muscle and the brain as well as to the liver and kidneys.

Exposure to chloropicrin causes less injury to the upper respiratory tract than chlorine, and more than phosgene. The damage induced by it in the medium-sized to small bronchi is great, with the result that an acute bronchitis develops early. Pulmonary edema also develops promptly, the effect of this agent resembling chlorine in that respect.

Exposure to mustard gas by inhalation of vapors produces acute injury and inflammation of the entire respiratory tract, followed by necrosis and desquamation of the mucous membrane and pulmonary epithelium. A diphtheritic membrane forms on a mucous surface, and a lobular pneumonitis develops, with plugging of bronchioles followed by the formation of bronchopulmonary abscesses that quickly come to the surface, inducing pleuritis and locular empyema. The generalized pulmonary edema associated with exposure to the agents classified as pulmonary irritants, is not a conspicuous part of the picture.

Clinical information on the effects of the inhalation of lewisite by human beings is not available. From observations on dogs it would seem that the type of injury and inflammation resembles that produced by mustard gas, with the exception that there is somewhat greater pulmonary edema. Secondary infection, bronchopulmonary abscess and bronchopneumonia develop promptly and are the most striking features of the pulmonary pathology. Petechial hemorrhages, and other toxic changes in the liver and kidneys give evidence of the general intoxication that might be expected to result from the absorption of this organic arsenical compound.

TABLE III

THE CLINICAL CHARACTERISTICS OF THE BLUE AND GRAY TYPES OF CYANOSIS

Symptom or Sign	*Blue or Florid Cyanosis*	*Gray or Pallid Cyanosis*
Respiratory rate	40—50	50
Pulmonary moisture	Present	Present
Arterial blood pressure	Normal or elevated	Low
Venous pressure	High	Low
Pulse	100—full	130—thready
Temperature	100—101	May be subnormal
Temperature of skin	Warm	Cold—clammy
Headache	Present	Present
Mental state	Restless and apprehensive	Restless and delirious

The clinical types of pulmonary edema that are more commonly referred to, in connection with the effects of exposure to the pulmonary irritants, are differentiated on the basis of the onset and the development of the picture without regard to the specific agent responsible for the injury, as (1) latent, (2) blue cyanotic and (3) gray cyanotic types. There is the more reason for employing this classification rather than that based on the specific agents, since the latter may well be used in mixtures.

1. The latent type has been referred to previously, especially in connection with the effects of phosgene. Despite the fact that the serious symptoms of pulmonary edema tend to develop soon after exposure in most instances, it is necessary to be on the lookout for exposed persons who appear to be practically free of symptoms only to develop labored respiration and circulatory embarrassment within a few hours. This condition may be revealed dramatically by the collapse of an individual who, having attempted some task involving moderate or even slight exertion, has exceeded his scanty respiratory reserve.

2. The type of case classified as having a "blue" cyanosis, is one in which the individual has an anoxemia sufficient to give rise to cyanosis, and obviously, therefore, is suffering from some degree of tissue anoxia. The degree of the anoxemia, and of the general anoxia, is difficult to estimate from the appearance of the patient, since the thickness and

color of the skin, the richness of the circulatory supply, the intensity and quality of illumination, and many other factors, influence one's observation. About 5 grams of reduced hemoglobin are required to produce cyanosis, and therefore, obvious cyanosis must be regarded as evidence of a significant degree of anoxia. The significance of the blue cyanosis, otherwise spoken of as purplish or florid cyanosis, has been pointed out in the discussion of the pathological physiology. The chief clinical characteristics of this state are summarized in Table III.

3. The "gray" cyanotic type is characterized less by the cyanosis, which may be difficult to see, than by the obvious ashen pallor which is associated with circulatory failure. It is thus referred to as the pallid type of pulmonary edema. The associated clinical phenomena of this condition, as given in Table III, show its grave character. When it appears early in the course of the illness, it denotes either extensive pulmonary damage, or the existence of a crippled circulatory system; when seen as a late manifestation, it is only slightly less ominous, since it shows cardiac weakness.

The Sequelae of Injury Induced by Pulmonary Irritants

The sequence of events following exposure to irritant agents has been indicated in sufficient detail to delineate the course of the clinical condition. Death may occur at any of the stages indicated, or the edema may clear up, the pneumonia may be resolved, and complete recovery, without residual effects of any kind may take place. The length of time required for this result depends upon the degree of pulmonary injury sustained and upon the nature of the complications that develop. In addition to the secondary infection which in some degree is almost inevitable, other factors such as age, chronic respiratory disease (bronchial asthma, chronic bronchitis, tuberculosis), diseases of the circulatory system, and trauma, must be considered in the case of civilian casualties.

The sequelae, likewise, will be influenced in frequency and severity by all of the factors mentioned above. The experience of the First World War has shown that complete recovery was the rule among young, healthy persons who survived the acute effects of exposure to pulmonary irritant gases. For a number of reasons the incidence of permanent disability may be expected to be higher among the unselected victims of gas attacks carried out against the general population, but such disability should be relatively infrequent if casualties can be given adequate

care at the proper time. Certain neuroses will be seen, if past experience can be relied upon, and the frequency of these will depend in large measure upon the extent to which the public is taught, led and advised in such matters. In other words, panic and unrestrained fear of mysterious and horrible effects that are thought to result from exposure to war gases, provides a fertile soil for the development of neurotic manifestations.

The sequelae that have been described among soldiers are pulmonary fibrosis, chronic emphysema, chronic bronchitis and bronchiectasis, all of which are the result of infection rather than chemical injury, together with two other disturbances, which in at least some instances are partially functional and which cannot always be clearly distinguished from each other. One of these, generally known as "effort syndrome," is very like "soldier's heart" and is so spoken of by some writers; the other is characterized by recurrent attacks of nocturnal dyspnea. In effort syndrome, as indicated in the expression, the patient becomes exhausted by an insignificant expenditure of effort. Headache, vertigo, precordial pain, dyspnea and tachycardia are the outstanding complaints. The attacks of nocturnal dyspnea are associated with little or no evidence of organic disease of the chest. There is usually an increase in the number of erythrocytes and in the hemoglobin content of the blood. This phenomenon suggests that there is chronic anoxia, due perhaps to rapid shallow breathing, but it is said that no cyanosis is present. Further study of cases of this type would seem to be required to elucidate their physiological background.

The Treatment of Pulmonary Irritation and Edema

First aid treatment of casualties consists of maintenance of quiet and warmth until transportation in the recumbent position can be accomplished. In view of the nature of the condition, persons regarded as casualties should not be permitted to walk or even to sit up, but should be moved on a stretcher as soon as possible to the point at which medical examination and treatment can be instituted. They should be covered up with blankets to prevent chilling, and in addition warm drinks may be administered if desired. Artificial respiration must not be given even to persons in acute respiratory distress, and decontamination should be limited to simple, quickly completed measures such as, clipping off the hair, cutting away clothing, and removal of any agent that may involve

obvious hazard to life or vision.

No treatment for the prevention or relief of pulmonary edema is available at present. Relief of the anoxia may be accomplished satisfactorily in many instances by the administration of oxygen. So long as cyanosis can be prevented by this means, this form of treatment is satisfactory, in that it combats the anoxia, prolongs life, and perhaps tides the patient over a critical period. The administration of oxygen may be carried out in various ways dependent upon the facilities available for the purpose. The use of a nasal catheter is perhaps the best when special equipment is not available. By this means the oxygen tension of the inspired air can be trebled. In well developed pulmonary edema, it may be necessary to resort to the administration of oxygen in a closed inhalation system under pressure. Self-contained portable and fixed inhalation equipment, and various types of masks are available for use with oxygen or with oxygen-carbon dioxide mixtures. The best results can be obtained only by carefully trained personnel. Indeed the success of any efforts made to employ oxygen therapy in this condition will depend upon the training and experience of attendants.

There is considerable disagreement as to the usefulness of venesection in the treatment of pulmonary edema. One may be dubious of the rationale of reducing the volume of the circulating tissue under conditions in which it is destined to be reduced by transudation from a large injured capillary bed. On the other hand, one may be justified in believing that the relief of the high venous pressure associated with the stage of florid or blue cyanosis is a valuable albeit a temporary measure. That any benefit can accrue from attempts at blood-letting in the stage of gray cyanosis, seems impossible.

Prevention and treatment of the infection that may follow this type of upper respiratory and pulmonary injury, will be indicated in accordance with the best methods available. The use of sulfonamide drugs may offer means, not formerly available, to cope with this formidable complication. Perhaps caution against an excess of optimism may be justified here, however, since the organisms involved in such infections will be those harbored in the nasopharynx of the victim, rather than those that would be expected in more common types of nasopharyngeal and pulmonary infections. Arsenicals may be indicated in pulmonary abscess with gangrene associated with spirochetal infections.

Other forms of treatment will be wholly non-specific and presum-

ably symptomatic. General supportive treatment, and careful avoidance of exertion are necessary. Apprehension should be relieved by persuasion as far as possible, but when anxiety and restlessness reach a stage where more vigorous control is required, the disadvantages associated with the use of sedatives, including morphine, will be counterbalanced by their beneficial effect. Heart stimulants may be required and should be used as indicated, caffeine being especially recommended.

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THE EFFECT OF WAR GASES AND OTHER CHEMICALS ON THE EYES OF THE CIVILIAN POPULATION*

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BECAUSE in total warfare many chemicals other than war gases may injure the eyes of the civilian population these as well as war gases will be considered in this paper. However special emphasis will be placed on the diagnosis and treatment of eye injuries by war gases.

WAR GASES

The first record of the use of noxious gases is by the Spartans against the Athenians in 431-404 B. C.[1] Gas was first used by the Germans in April, 1915, in a surprise attack against the Allies in Flanders. The casualties were high because the troops had no protection. Since gas was found to be an efficacious military weapon its use became widespread during World War I but fortunately efficient protection was rapidly developed. More recently gas was reportedly used by the Japanese against the Chinese and by the Italians in Ethiopia when mustard gas oil was sprayed from airplanes. It is possible that the horrors of gas warfare will be brought to the general population at some time in the future even though there is a question of how efficacious such use of gas may be in winning a war.

Although we have little information concerning the effect of war gases on the civilian population, we do know much concerning the effect of these gases on the eyes (1) from experience in the last war, (2) from accidents in factories manufacturing war gases and (3) from experiments with animals. These three sources of information have been

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TABLE I

CHART SHOWING NUMBER AND PERCENTAGES OF CASES OF BLINDNESS IN WORLD WAR I FROM GAS AND NON-GAS WEAPONS (GILCHRIST[2])

Nature of Injury	*Cause*	*Number*	*Per Cent*
Loss of right eye	Gas	16	1.9
	Non-gas	307	37.8
Loss of left eye	Gas	10	1.2
	Non-gas	289	35.6
Loss of both eyes	Gas	4	.5
	Non-gas	44	5.3
Loss of one eye (unknown)	Gas	3	.4
	Non-gas	59	7.3
Traumatism	Gas	0	.0
	Non-gas	80	10.0
Total	Gas	33	4.0
	Non-gas	779	96.0

used in preparing this outline of injuries of the eyes which might be expected if gas warfare is brought to the civilian population.

On the whole, war gases have not proved to be very harmful to vision in a permanent way. In World War I of 812 blind or partially blind soldiers, 4 per cent of the injuries were the result of gas weapons while 96 per cent resulted from non-gas weapons. Gilchrist[2] has tabulated these cases in Table I.

Derby's[3] experience in World War I showed that from 75 to 80 per cent of the eyes affected by gas were only mild cases. Parlange[4] reported the following incidence of eye affections: three corneal ulcerations in 1500 gassed individuals; two corneal opacities in 1800 gassed individuals and 700 conjunctivitides in 4000 gassed individuals.

For practical purposes all known gases may be divided according to their actions into five groups: (1) vesicant, (2) lung irritating, (3) sternutatory, (4) lacrimatory and (5) toxic gases.

Many known war gases are capable of causing irritation, and direct or indirect injury to the eyes but practically mustard gas and lewisite are the only important ones from the standpoint of direct eye injuries. Individuals with previous eye lesions, e. g., trachoma, keratitis or old

corneal scars, suffer more acutely from contact with gas than do persons with normal eyes.[4] It is sometimes difficult to be sure to which gas a person has been exposed and shells combining mustard, phosgene and tear gas were used in World War I.[5] Another method of using gas at the time of the last war was to release shells containing sternutatory gases which would force the soldiers to remove their masks and then to release lung irritating gases. At that time the respirators afforded no protection against sternutatory gases, but present masks do since a paper filter was inserted.

Vesicant Gases

Mustard Gas: In the first World War mustard gas was used in shells and in the Ethiopian war as a spray from airplanes. Probably an attack on the civilian population would be in the latter form.

Mustard gas is also known as yperite (French) or yellow cross (German). It is known as mustard gas because of its odor and as yperite because the Germans first used it at Ypres in July, 1917. The term yellow cross is derived from the symbol used by the Germans to designate the shells containing this gas.

Mustard gas is a dark brown liquid (dichlorethylsulphide, $[(C_2H_4Cl)_2S]$, with a high boiling point (214 degrees F.) and changes slowly into a colorless gas. This gas is one of the most difficult with which to cope because earth on which the oil has fallen remains permeated for from three days to a week. The length of time depends upon the weather. Rain neutralizes the soil within three days and dry weather permits the gas to remain potent for at least a week.

Eye casualties can occur (1) as a result of direct splashing of the oil into the eyes, (2) by direct transfer from the hands to the eyes after contact with the earth, clothing or other objects and (3) by vapors. The latter is by far the most frequent.

The ocular symptoms following contact with the *vapors of mustard gas* occur only after four to six hours. Although the symptoms are severe there are no serious or permanent ocular lesions in the usual conditions of warfare, but if the eye is exposed to high concentrations the cornea can be severely damaged as experimental work has shown.

Hyperemia of the conjunctiva accompanied by tearing, photophobia and blepharospasm, appears approximately four to six hours after contact. The pain becomes very severe about eight hours after exposure to the

gas and edema of the eyelids develops. The appearance is similar to that of infectious conjunctivitis. The eyelids are swollen and in attempting to separate them with the aid of a retractor, a cloudy fluid is expressed. The conjunctiva is red with marked chemosis. In severe cases, the lower fornix is red but the part of the conjunctiva exposed between the eyelids can be porcelain white. Corneal lesions are usually discrete, but epithelial desquamation may often be revealed by fluorescein. The exposed part of the eyes between the eyelids is most affected by the vapors.

If proper treatment is administered, and frequently without treatment, edema of the eyelids disappears in a few days. Hyperemia, photophobia and tearing still persist for a week or two. Blepharospasm and photophobia may be present even longer in severe cases.

When there is *direct contact with the mustard oil* the ocular lesions are much more severe with corneal ulcers and sometimes even with perforations of the cornea. The skin and eyelids may present first degree or even second degree burns.

Late Conjunctival Complications: The conjunctiva may remain very sensitive to all irritants (wind, dust, light, etc.) and attacks of blepharoconjunctivitis often occur. In exceptional cases epiphora caused by cicatricial obliteration of the lacrimal puncta has been noted. Symblepharon may develop in some cases. There may be abnormal vascularization characterized by the persistence of conjunctival vessels of carmine color. Biomicroscopically, true varices of the conjunctiva may be seen near the limbus years later.[6]

Late Corneal Complications: The cornea in most cases returns to normal. In others leukomas develop and recurrent ulcers of the cornea have been observed after several years.[7] These serious and lasting corneal lesions may be seen especially if direct contact with the mustard oil (splash) has occurred or transfer by the fingers has been possible, but are rare if there has only been contact with the vapors of the gas.

Intra-ocular Complications: In severe mustard gas burns of the body, Beauvieux[8] and Genet and Delord[6] noted dilatation of the retinal veins and hyperemia of the disk. In his experimental work on monkeys Wessely[9] also noted some retinal hemorrhages and he believed that they were due not to the general intoxication, but to the local penetration through the burned ocular tissues; such hemorrhages occurred only in those animals which had not had a protective ointment introduced in

their eyes prior to the instillation of mustard gas oil.

Prognosis: Generally the prognosis in cases of mustard gas burns is benign. Beauvieux[8] observed only two cases in 1,800 mustard gas casualties in which severe corneal ulceration developed and even these regained useful vision.

Tissue which previously has been affected by mustard gas is susceptible to smaller concentrations of the vapor.[10]

Treatment of Mustard Gas Burns of the Eye: Although eyes that have been exposed to the vapors of mustard gas may at first look severely damaged, the prognosis is good and most cases will recover entirely even if no treatment is applied to the eyes. Especial care should be taken to avoid secondary infection and it is, therefore, better to apply no treatment at all if sterile solutions and drops are not available.

But if the eyes have been splashed by mustard gas oil, it is important to irrigate the eyes as soon as possible. The immediate and copious use of water, advised by Pellathy,[11] to lessen the action of mustard gas on the eyes because of the difficulty in obtaining proper solutions quickly, may well be the most important first aid treatment, and should be used as early as possible, preferably within fifteen minutes since most of the mustard gas has been absorbed by that time.

The patient should be assured that sight will be restored and if possible the eyelids should be separated permitting him to see. Pontocaine (½ per cent) should be instilled once or possibly twice if it is necessary to relieve pain or to temporarily separate the eyelids, but cocaine and atropine should be avoided. Ointments should not be used in the treatment of mustard gas injuries for the first few days until the chemical has been completely eliminated from the tissues since mustard gas is absorbed by any fatty substance and it is thus kept in contact with the eye. No dressing should be applied.

The eyes may be washed with alkaline solution (sodium bicarbonate 2 to 5 per cent) or neutralizing solution (dichloramine-T). Dichloramine-T may be used in 0.5 per cent solution.[12] It must be dissolved in an organic solvent (chlorinated paraffin or chlorinated diphenylether), and a local anesthetic should be instilled prior to irrigation. Hypertonic solutions* have been recommended because it is claimed they induce drainage by osmosis, thus hastening elimination of the gas.[13] Livingston

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* Saturated aqueous solution of sodium sulphate 800 grams, Simple syrup 200 grams *or* Magnesium sulphate 40 grams, Simple syrup 50 grams, Water 150 grams

and Walker[14] reported that saturation of the system with ascorbic acid, given intravenously in four rabbits, proved to have a remarkable effect in preventing the spread of keratitis and the progress of the eyelid inflammation resulting from mustard gas. However, Mann and Pullinger[15] stated that intravenous injections of ascorbic acid neither prevent nor influence mustard gas lesions of the eyelids, conjunctiva or cornea. Pickard[16] advised the external application of mercurial salve to the eyelids in order to prevent chalazia, hordeola, and small multiple abscesses of the eyelids. However, it seems better to use no antiseptics since all are irritating to the tissues and since, notwithstanding the appearance, there is no infection if the eye is properly treated.

During convalescence zinc or boric acid solution may be instilled. Tinted lenses may also be prescribed.

Experiments with Mustard Gas on Animals: Our experiments with rabbits*† have demonstrated that the ocular lesions are extremely severe if even the smallest amount of liquid mustard gas is applied to the cornea, and the tissues seldom heal with little scarring as reported by other workers, even if immediate or subsequent treatment is administered. The use of a 5 per cent sulfanilamide-sulfadiazine ointment (equal parts) applied three days after instilling liquid mustard gas does not retard healing and may tend to prevent or control secondary infection. However, we have not used dichloramine-T which Heinsius[17] claims will prevent damage if the eye is flushed within the first fifteen minutes after mustard gas is applied.

Lewisite: Lewisite (Cl CH:CHAsCl_2) was prepared for use in the last war but was never liberated. It is a heavy, oily liquid, colorless in its pure state but dark upon standing. From experimental studies, its action is similar to that of mustard gas but more destructive. According to Hughes[18] the onset of symptoms following contact either with the vapor of lewisite or the liquid is almost immediate. His experiments with rabbits showed that within an hour there is marked edema of the conjunctiva and a definite clouding of the cornea. After a few hours, necrosis of the conjunctival vessels with the formation of hemorrhagic area is quite striking and a marked fibrinous iritis develops. Hughes states that in general the subsequent course of the lewisite lesions shows more corneal edema, more intense vascularization of the cornea and

* de Gara, P. F., Loutfallah, M. and Berens, C. under a grant from The Ophthalmological Foundation, Inc. and The John and Mary R. Markle Foundation, Inc. at Cornell University Medical School.
† Mustard gas furnished through the courtesy of Dr. Kenneth C. Blanchard, Department of Biology, New York University.

more tendency to purulent exudation and corneal ulceration than is the case of mustard gas burns.

Treatment: The treatment is probably the same as for injuries caused by mustard gas but we have had no experience with it. The use of copious irrigations with water or a 1.5 per cent solution of sodium bicarbonate is recommended. Hughes[18] states that except for the use of chlorinated solutions, the treatment of lewisite burns is essentially that of mustard gas. Hydrogen peroxide and potassium permanganate for the treatment of lewisite burns have been discarded generally.

Lung Irritating Gases

Although the lung irritating gases are the most serious because of their lethal action, they are not so important from the standpoint of the ophthalmologist. However, these gases, which include chlorine, chloropicrin (CCl_3NO_2), and phosgene ($COCl_2$), are irritating to the eyes. Phosgene may be associated with intra-ocular hemorrhages which probably are secondary to the anoxemia resulting from pulmonary edema.[5]

Sternutatory (Sneezing) Gases

The sternutatory gases are in reality solids of the arsine chemical group and include diphenylarsine [$(C_6H_5)_2As$], diphenylamine-chlorarsine (Adamsite), diphenylchlorarsine [$(C_6H_5)_2AsCl$], and diphenylcyanarsine [$(C_6H_5)_2AsCN$]. These chemical substances cause irritation of the eyes with excessive lacrimation. Sneezing is the essential symptom, but nausea and vomiting as well as severe headaches also occur.

The eye symptoms are usually of short duration and after a few minutes the effects have passed.

Lacrimatory Gases

Lacrimatory gases include chloracetophenone* ($C_6H_5COCH_2Cl$) (a white crystalline solid), benzyl bromide ($C_6H_5.CH_2Br$)†, chloro-acetone ($CH_3.COC_6H_4Cl$)† and bromacetone ($Br.CH_2CO.CH_3$)†. The ocular symptoms resulting from the use of lacrimatory gases are: burning pain, excessive lacrimation, injection of the conjunctiva and photophobia and in rare cases, when the gas is splashed into the eyes, free exfoliation of the epithelial covering of the cornea. Itching, burning.

* Common tear gas used in police work.
† These last three chemicals are in liquid form.

tearing, blepharospasm and photophobia are so intense that those affected are incapable of finding their way without aid. The bulbar and palpebral conjunctivas are markedly hyperemic but there is no ciliary injection. These symptoms appear immediately after exposure to the gas and disappear within a few minutes or hours, leaving no trace except when splashed into the eyes; then the burn is similar to that produced by strong acids.

Prognosis: So far as the eye is concerned, lesions produced by lacrimatory gases are benign unless the liquid is splashed into the eye. Schmidt[19] reported a case in which tear gas (brommethylethyl ketone), which is generally considered harmless and to cause only transient irritation, was shot into an eye and produced severe destruction and permanent damage deep in the orbital tissues.

Treatment of Injuries Caused by Lung Irritating, Sternutatory and Lacrimatory Gases

The patient should be removed from the contaminated area. Even if nothing is done all eye symptoms usually disappear rapidly. Therefore, useless treatments which may cause infection if nonsterile solutions are used should be avoided. If warm sterile solutions are available the eyes should be flushed, e.g., with sodium chloride 1.4 per cent, sodium bicarbonate 2 to 5 per cent or boric acid 2 per cent. Sodium sulfite has been recommended by McNally[*5] to neutralize and dissolve lacrimatory gases. If pain is severe a sterile solution of pontocaine (½ per cent) may be instilled once or twice; if irritation persists light liquid petrolatum may be instilled.

If liquid was splashed into the eye immediate irrigation is necessary. Water should be used if no other sterile or nonirritating solution is available.

Systemic Toxic Gases

The systemic toxic gases include hydrocyanic acid, cyanogen chloride and cyanogen bromide. These gases are usually fatal in a few seconds or at most minutes. However, there are rare examples of blurring of vision and irritation of the eyes in exceptional cases surviving such an attack.

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* Sodium sulfite 0.4 gm.
Water 25.0 cc.
Glycerin 75.0 cc.

Carbon monoxide is not used in chemical warfare but great quantities of it are produced when a shell explodes or when a machine gun or a cannon is fired. Intoxication can, therefore, be observed in badly ventilated dugouts or pill boxes.

Other Chemicals that May Affect the Eyes as a Result of Total War

In addition to the gases from bombs or those that may be sprayed, civilians and workers may be exposed to a great number of chemicals. If bombs fall in the kitchen or in the shop, these chemicals may easily affect the victims' eyes. These substances which are the same as those encountered in industrial casualties may cause severe eye injury.

For example, caustic soda and caustic potash lyes as well as other alkalies produce lesions of the conjunctiva and cornea. Metal workers, rubber workers and chemical workers are especially exposed to these agents. Acrolein and ammonia used in refrigerating plants and in refrigerators are important because of the severity of the eye injury when there is direct contact, e.g., necrosis of the cornea. Battery acid is another hazard which might have to be considered in addition to sulphuric, nitric and other acids which cause severe burns of the conjunctiva, cornea and eyelids.

Acid Burns: Acid burns may cause immediate injury to the conjunctiva and cornea. The prognosis depends upon the amount and concentration of acid contacting the eye, and how long it acted.

Alkali Burns: Alkali burns may cause progressive injury of the eye. Strong solutions penetrate the cornea in a few minutes causing desquamation. Dense opacities follow with pannus. Penetrating ulcer of the cornea may be a sequela.

Immediate First-Aid Treatment of All Chemical Burns: The conjunctiva is flushed. The urgency of immediate treatment does not permit a special solution being made up. Therefore, the eyes should be flushed with water and a sterile nonirritating oil (liquid petrolatum) instilled, if available. The patient should then be referred to a specialist for appropriate treatment, for example, atropine for iritis, cauterization for corneal ulcers.

Special Treatment of Acid Burns: A solution of sodium bicarbonate (2 per cent) effectively neutralizes corrosive acids. Subsequent treatment depends upon the individual symptoms encountered. The follow-

ing have been recommended: boric acid ointment and an eye pad, liquid paraffin, cod liver oil, and mild silver protein (10 per cent) followed by a 2 per cent solution of boric acid.

Special Treatment of Alkali Burns: Treatment includes flushing the eye with water, saline solution (1.4 per cent) or boric acid (2 per cent). The instillation of an isotonic acetate buffer solution* neutralizes any excess alkali.[5] Further treatment may include: atropine sulfate, 1 per cent solution, three times a day to control secondary iritis and breaking adhesions between the eyelids and eyeball by means of a glass or plastic spatula and boric acid ointment passed into the upper and lower conjunctival culs-de-sac twice a day. Secondary infection may be prevented or combatted by the instillation of a mild silver protein (10 per cent) followed by irrigation with saline solution (1.4 per cent) or the application of sulfadiazine ointment (3.5 per cent).† The immediate application of rabbit peritoneum has been recommended by Brown[20] as a protective membrane to separate the cornea from the burned palpebral conjunctiva following most corrosive chemical burns.

At a later date, the excision of superficial corneal scars or keratoplasty may be required to restore vision when the corneal scars obstruct the pupil. If adhesions form between the conjunctiva and the eyeball (symblepharon) conjunctivoplasty may be indicated. If secondary glaucoma develops it is difficult to control and may require the injection of alcohol into the ciliary ganglion. If useful vision may be restored 1 cc. of 40 per cent alcohol may be injected into the ganglion after 1 cc. of novocain (2 per cent solution) has been injected and the needle left in place. If vision is destroyed, 80 per cent alcohol (1 cc.) may be injected.

Lime burns should receive continued treatment until all danger of cicatricial contraction of the conjunctiva and secondary opacification of the cornea is past. This type of injury tends to involve the deeper layers of the cornea and sclera, even when the eye appears to be only slightly affected, causing an associated iritis.

Complications of Burns Caused by Acids and Alkalies

Complications which must be looked for and if possible prevented

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* Acetic acid 2.5 gm.
Sodium acetate 3.0 gm.
Sodium chloride 4.5 gm.
Distilled water 1000.0 cc.

† Sodium sulfadiazine in aquaphor 3.5 per cent

are: corneal ulcers, iritis, glaucoma and adhesions between the conjunctiva and the eyeball.

Summary and Conclusions

Although vesicant, lung irritating, sternutatory and lacrimatory gases are expected to cause casualties, physicians must be prepared for new unknown gases. For example, arsenated hydrogen, a hemolytic gas, was considered a possibility in the fall of 1939.

Physicians are urged to remember that applying no local eye treatment will usually do less harm than using medication which may damage the eyes or solutions or instruments that are not sterile, as secondary infection is the principal danger from the external application of the war gases.

The immediate treatment of all gas and chemical injuries of the eyes is to flush the conjunctival culs-de-sac with water or a sterile solution of salt (1.4 per cent). If acid is known to have caused the burn, sodium bicarbonate (2 per cent solution) should be used. If an alkali, the conjunctival culs-de-sac should be flushed with boric acid (2 per cent solution). The immediate instillation of light liquid petrolatum is useful and contraindicated only in mustard burns. Severe pain may be controlled by instilling pontocaine (0.5 per cent solution) or butyn (1 per cent solution) once or twice but it is preferable to control pain with internal medication (morphine, allonal, etc.) as most local anesthetics have a deleterious effect on the corneal epithelium. Secondary infection should be combatted with mild silver protein or sulfadiazine solution or ointment (3.5 per cent). Iritis should be suspected in all severe burns and treated with atropine solution or ointment unless secondary glaucoma develops. Ulcers of the cornea and the secondary corneal scarring also symblepharon may require surgical treatment.

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DEATHS OF FELLOWS

FRASER, JOHN FRANK: 100 Central Park South, New York City; born in West River, Canada, January 8, 1867; died in New York City January 31, 1943; graduated in medicine from Bellevue Hospital Medical College in 1892; elected a Fellow of the Academy May 2, 1918.

Dr. Fraser was consulting dermatologist to the Memorial Hospital, the New York Post-Graduate Hospital and the St. Francis Hospital at Port Jervis; a diplomate of the American Board of Dermatology and Syphilology; a member of the American Academy of Dermatology and Syphilology; a Fellow of the American Medical Association and a member of the State and County Medical Societies.

HARRIS, THOMAS JEFFERSON: 104 East 40 Street, New York City; born in Claremont, New Hampshire, July 26, 1865; died in Northport, Long Island, New York, March 14, 1943; graduated in medicine from the University of Pennsylvania in 1889; elected a Fellow of the Academy January 4, 1894.

Dr. Harris was consulting otolaryngologist to the New York Post-Graduate Hospital and at one time served as professor of diseases of nose and throat at the New York Post-Graduate Medical School. He was a diplomate of the American Board of Otolaryngology, a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, and a member of the American Laryngological, Rhinological and Otological Society and its president 1916-1917, the American Laryngological Association, the American Otological Society and its president 1925-26, and the State and County Medical Societies.

HYAMS, JOSEPH ANDREW: 78 East 79 Street, New York City; born in this city, May 15, 1884; died in this city, January 26, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1905; elected a Fellow of the Academy May 2, 1918.

Dr. Hyams was attending urologist and director of the urological service at the New York Post-Graduate Hospital; attending urologist to the Reconstruction Hospital; consulting urologist to the Beth David Hospital, All Souls Hospital at Morristown, New Jersey, Community Hospital, St. Francis Hospital at Port Jervis; and director of urological service at the Gouverneur Hospital. He was a Fellow of the American College of Surgeons, the American Medical Association, a diplomate of the American Board of Urology, a member of the American Urological Association and the State and County Medical Societies.

LAIGHTON, FLORENCE MARION: 37 West 72 Street, New York City; born in Portsmouth, New Hampshire, December 21, 1870; died in New York City, January 15, 1943; graduated in medicine from the Woman's Medical College of the New York Infirmary for Women and Children in 1898; elected a Fellow of the Academy, May 19, 1907. Dr. Laighton was a member of the American Medical Association and the State and County Medical Societies.

LICHTWITZ, LEOPOLD: 667 Madison Avenue, New York City; born in Ohlau, Silesia, Germany, December 9, 1876; died in New York City, March 18, 1943; graduated in medicine from the University of Leipzig, Germany, in 1901; elected a Corresponding Fellow of the Academy February 4, 1932, and on March 2, 1939 was elected a Fellow.

Dr. Lichtwitz was professor of clinical medicine at Columbia University for the last eight years and chief of the medical division at the Montefiore Hospital for ten years. Prior to his coming to the United States in 1933, he was for two years on the staff of the Rudolf Virchow Hospital in Berlin, and from 1917 to 1931 he was director of the City Hospital in Hamburg. He was a former president of the German Society for Internal Medicine, an officer of the German Society for Gastroenterology and Metabolic Diseases and an officer of the Society for Internal Medicine, Berlin.

MILLS, JACKSON MIHALOVITCH: 136 East 57 57 Street, New York City; born in Detroit, Michigan, May 24, 1863; died in New York City, March 18, 1943; graduated in medicine from the Vanderbilt and Nashville Medical College in 1884; elected a Fellow of the Academy November 7, 1901. He was also a member of the State and County Medical Societies.

PAULSEN, ALICE ELIZABETH: 15 Merrian Avenue, Bronxville, New York; born in New York City, February 15, 1890; died in Hillside, New York, March 16, 1943; received the degree of Ph.D. from Columbia University in 1924; elected an Associate Fellow of the Academy February 3, 1927; and served in research from 1927 to 1937 with the Committee on Public Health Relations.

STEINER, WALTER RALPH: 646 Asylum Avenue, Hartford, Connecticut; born in Frederick, Maryland, November 18, 1870; died in Hartford, Connecticut, November 4, 1942; received his Master of Arts degree at Yale University in 1895; graduated in medicine from the Johns Hopkins University School of Medicine, Baltimore, in 1898; elected a Fellow of the Academy January 5, 1933.

Dr. Steiner was consulting physician to the Hartford Hospital since 1934, and chairman of the medical and surgical staff from 1925 to 1933, having joined that institution in 1901 and serving in numerous capacities. He was also consulting physician to the Hartford Orphan Asylum, Bristol, New Britain General, Meriden, Middlesex (Middleton) and the Charlotte Hungerford hospitals, Torrington, and honorary physician to the Manchester Memorial Hospital.

Dr. Steiner was a Fellow of the American College of Physicians, a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and, except for a few sessions, a member of the House of Delegates from 1919 to 1940, a member of the American Association of Pathologists and Bacteriologists, and a member of the Association of American Physicians, American Clinical and Climatological Association and its president from 1934 to 1935, Medical Library Association and its president from 1931 to 1933, American Association of the History of Medicine and its president from 1937 to 1939, Congress of American Physicians and Surgeons and its secretary from 1911 to 1932, and the Connecticut State Medical Society, as its secretary from 1905 to 1912, chairman of its council from 1929 to 1933, and its president from 1934 to 1935.

In 1937 the Hartford Medical Society, which he served as Librarian from 1903 to 1941 and president in 1929, named its Library the Walter R. Steiner Medical Library in his honor.

Dr. Steiner made numerous contributions to literature on internal medicine, pathology and medical history.

STEVENS, CHARLES WADHAMS: 170 West 74 Street, New York City; born in Albany, New York, November 12, 1867; died in New York City, March 15, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1892; elected a Fellow of the Academy April 3, 1919. He was a member of the State and County Medical Societies and for many years was on the staff of the New York Post-Graduate Medical School and Hospital.